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Cleveland Clinic Quarterly

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A Bulletin Published by

The Staff of the Cleveland Clinic

CLEVELAND, OHIO

Vol. 5 JULY, 1938 No. 3

CONTENTS

The Frank E. Bunts Institute 155

Transplantation of Endocrine Tissue: Preliminary Report on Experimental Work.
William E. Lower, M. D., Department of Genito-Urinary Surgery 156

The Use of Sulfanilamide in the Treatment of Chronic Ulcerative Colitis: Preliminary Report of 11 Cases.
E. N. Collins, M. D., Section on Gastro-Intestinal Diseases 161

The Paraffin Bath.
Walter J. Zeiter, M. D., Department of Physical Therapy 170

Choked Discs Associated with Otitis Media: An Explanation of the Mechanism in Certain Cases.
W. James Gardner, M. D., Department of Neurosurgery 176

The Treatment of Extrasystoles.
A. Carlton Ernstene, M. D., Secton on Cardio-Respiratory Diseases 181

The Interpretation of Qualitative Changes in Neutrophilic Leukocytes. "Shift to Left"—"Shift to Right"—"Toxic" Granulation.
Russell L. Haden, M. D., Section on General Medicine 184

Celiac Ganglionectomy in Raynaud's Disease: Further Report.
George Crile, M. D., Department of Surgery 195

Biophysical Foundations of Supervoltage Roentgen Therapy.
Otto Glasser, Ph.D., Department of Biophysics 196

Diaphragmatic Hernia.
Joseph C. Root, M. D., Department of Roentgenology and Clark P. Pritchett, M. D., Fellow in Medicine 203

Rhinophyma: Report of a Case.
R. S. Dinsmore, M. D., Department of Surgery and K. W. Keller, M. D., Fellow in Surgery 217

Migraine in a Patient with Essential Hypertension: Report of a case.
C. R. K. Johnston, M. D., Department of Allergy 221

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THE FRANK E. BUNTS INSTITUTE

announces

A Course In

General Diagnosis and Treatment

on

MONDAY, TUESDAY, and WEDNESDAY
NOVEMBER 7, 8, and 9, 1938

and

A Course In

Diseases of the Eye, Ear, Nose, and Throat

on

MONDAY, TUESDAY, WEDNESDAY,
THURSDAY, FRIDAY, and SATURDAY
DECEMBER 5, 6, 7, 8, 9, and 10, 1938

Descriptions of these courses and outlines of the subjects to be covered will be published in the October, 1938, Quarterly.

TRANSPLANTATION OF ENDOCRINE TISSUE

Preliminary Report on Experimental Work

WILLIAM E. LOWER, M.D.

When an endocrine gland is destroyed by disease or operation, treatment, in most cases, comprises substitutional therapy administered orally or by injection and this generally must be continued for the remainder of the patient's life. In these cases, substitution of a functional gland is the desideratum for which everyone hopes.

The successful transplantation of tissues, however, is not a simple matter and depends upon a large number of factors, some of which concern the graft itself and others the host. To any graft, for example, a host may set up a natural defense reaction to injury or the introduction of a foreign body. Other factors of great importance are related to proper vascularization of a graft and the age, time, and relation of the transplant to the host. In considering the relation of the transplant to the host, there arise such questions as the auto-, homo-, or hetero-plastic character of the tissues and the genetic compatibility between tissue and host. Loeb and Wright[1] have stressed the importance of considering the genetic constitution of both donor and recipient.

Studies of sub-human animal grafting have almost invariably shown that hetero-transplantation, that is, transplantation between different species, is unsuccessful. Such studies lead one to regard with caution

FIGURE 1: Host: Castrated male rat. Ear in foreground shows testis from rat one day old, transplanted four months previously. Ear in background shows prominence made by seminal vesicle grafted simultaneously with testis.

the announcement that hetero-glandular grafting in human beings has brought favorable returns (Voronoff[2]).

Homoplastic grafting in human subjects is a more logical procedure than hetero-grafting. The preliminary studies of Stone, Owing, and Gey and more recently those of Gey[3] who used the tissue culture technic, offer considerable promise. Gey has reported that more than one-third of a series of 16 patients with marked parathyroid tetany are well from 2 to 6 years after homologous grafting with tissue cultures.

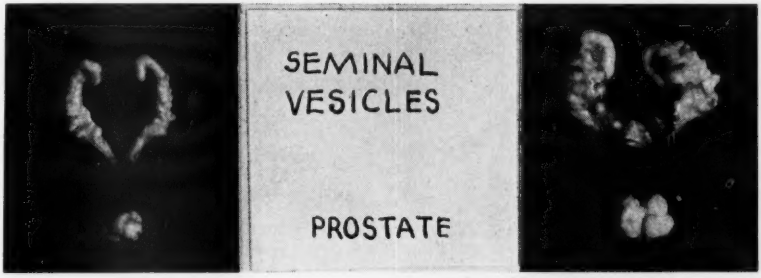

FIGURE 2: A: From a castrated male rat.

FIGURE 2: B: From a castrated male rat with a functional testis graft in the ear. Tissue from a rat one day old had been grafted two months before photograph was taken.

In well documented works (Werner[4]), the scanty literature dealing with successful transplantations in human subjects attests to the relatively little knowledge there is about this subject. On the other hand, there is a vast literature on the subject of transplantations in subhuman animal forms. Much information has derived from studies on transplantations of glands in rats. The studies to be reported here have been made on the rat, the technical work and the follow-up studies having been done by Eugene and Elizabeth Cutuly.

In our work, the first factor to be considered was determination of a suitable site for grafting of the glands. The tip of the ear seemed satisfactory because it readily afforded a good supply of blood and because the growth of a transplant could be watched from day to day.

Grafting to the ear is a comparatively simple procedure. About midway between the tip and the base of the dorsal side of the ear a short incision is made through the skin. The blades of scissors are inserted through this incision into the subcutaneous tissues and spread apart gently a number of times until a subcutaneous pocket has been formed. Tissue to be grafted is inserted through the opening of this pocket and gently pressed toward the tip of the ear. Sutures are not needed to keep

FIGURE 3: Host: Castrated male rat. Seminal vesicle graft in ear transilluminated to show secretion (light areas.) Flashlight bulb in background. This graft was stimulated by hormone from a testicular graft in the other ear.

the grafts in place or to close the slit in the skin. Usually, there is a little hemorrhage around the graft, but this does not seem to be injurious.

By this method, we have made more than 100 grafts into the ears of rats. All experiments in which adult tissues were used as transplantation material gave negative results. We have, however, had remarkable success with grafts from newly-born donor rats. The following tissues have been grafted: testis, prostate, seminal vesicle, pituitary, ovary, adrenal, thyro-parathyroid, and pancreas.

Testis grafts have taken well both in castrated hosts (30 out of 40 cases) and in normal hosts (20 out of 30 cases).

Accessory sexual organs, such as seminal vesicles, have grown in the presence of testicular male hormone (3 cases out of 3) but have uniformly failed to grow in castrated animals (10 cases).

Adrenal grafts have also uniformly failed to take in normal animals, but one adrenalectomized animal, bearing a homoplastic adrenal graft in the ear, is still alive more than one month after adrenalectomy.

Two thyro-parathyroid grafts have taken in normal animals.

In six cases of ovarian grafts, distinct nodules have formed at the site of transplantation, but where the hosts are spayed females, these nodules have apparently not been functional, as the spayed animals have not yet shown estrous vaginal smears.

Our results with transplants of the pituitary and pancreas are at present indefinite.

At the present time, we are interested primarily in reporting some of the results obtained with testis grafts.

Testes which have been grafted to the ears of castrated rats (Fig. 1) develop and produce male hormone, as judged by the return of the host's atrophied accessory organs toward a normal condition (Fig. 2), or by stimulation of grafted accessory sexual tissue (Fig. 3). Since male hormone is elaborated by the interstitial component of the testes, it would be expected that the graft seen in figure 1 would possess normal interstitial cells. This is confirmed histologically in figure 4. This experiment establishes the fact that a testis grafted in a subcutaneous pocket in the ear will produce sufficient male hormone to stimulate the seminal vesicles and prostate.

It is known that testes transplanted to other subcutaneous sites, as well

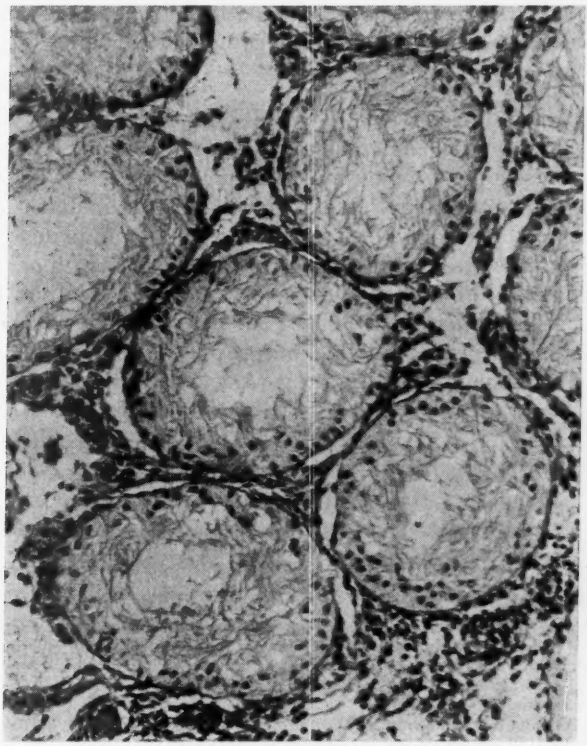

FIGURE 4: Testis from rat one day old taken from ear of a castrated host four months after transplantation.

as those transplanted to the scrotum, also may become functional. Scrotal grafts of testes differ from subcutaneous grafts in that the former may produce mature spermatozoa, as well as functional interstitial cells. Testes transplanted subcutaneously or intraperitoneally have never been known to develop spermatozoa (Moore[5]). This brings up one of the fundamental concepts concerning testicular physiology.

In most mammals, a scrotum is absolutely essential to spermatogenesis. Perhaps it would be more accurate to say that it is the thermoregulation effected by the scrotum which is essential to spermatogenesis. There is some evidence, in fact, which indicates that spermatozoa may develop in testicular tissue growing outside the scrotum—in the anterior chamber of the eye (Turner[6]). However, it was shown in these studies that the temperature of the anterior chamber of the eye is quite similar to that which obtains in the scrotum. It is hoped that the tip of the ear, too, may in some way be made to provide testis grafts with an environment favorable to spermatogenesis. While this has not been possible thus far, it may be that grafts transplanted for periods longer than four to six months will show some activity of the germ cells. Studies to determine this question are in progress.*

Summary

The material presented here is preliminary. Thus far it has been our purpose to develop a technic which will yield consistently good returns. When this has been accomplished, data will have accumulated which can be used as a standard for future studies. It is our plan to study in greater detail factors which are concerned in the successful or unsuccessful incorporation of grafted endocrine tissue in related and unrelated hosts. It is hoped that the results of our investigations will help in the understanding of principles which may apply to the problem of transplantation in human beings.

* There is some recent evidence which indicates that some germ cell development can occur in testis tissue grafted in the ear. Microscopic examination of a testis from a newborn rat grafted to the ear and removed several months later revealed the presence of spermatogonia and primary spermatocytes in the tubules.

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THE USE OF SULFANILAMIDE IN THE TREATMENT OF CHRONIC ULCERATIVE COLITIS

Preliminary Report of 11 Cases

E. N. Collins, M. D.

In the consideration of a new form of therapy for chronic ulcerative colitis it is well known that one year's experience and its use in eleven cases does not justify a final appraisal. The natural remissions of symptoms characteristic of this disease have been responsible for inaccurate appraisal of treatment in the past, unless evaluated in terms of repeated examinations over years of time and by independent investigators. On the other hand, this is an unusually serious disease and when the initial response to a new form of treatment is unusually favorable, we believe others should have the advantage of this experience before awaiting final appraisal.

In our experience, cultures made from rectal scrapings and stools have so commonly shown the presence of various strains of streptococci that a therapeutic trial with sulfanilamide seemed logical.

In eight of our eleven cases we found the initial response to sulfanilamide therapy more satisfactory in a shorter period of time than has been our experience with other forms of medical treatment. Since the progress proctoscopic examinations have revealed unexpected improvement if not normal findings, without scar formation, we believe this group of patients must have had unusually superficial involvement of the wall of the rectum and colon. Heretofore, although the patient had had a complete remission of symptoms, if a proctoscopic examination were done during the remission, the findings were unfortunately too often the same as those visualized at the time of the acute exacerbation of the disease.

The "regional" or so-called "right-sided" form of chronic ulcerative colitis has been encountered in 7 per cent of our cases. Operative procedures early in the course of the disease are the therapeutic methods of choice in these instances. The present communication deals with the remaining 93 per cent, the so-called "universal type," wherein the disease starts as a diffuse inflammation of the rectal mucosa and extends upward in the colon. When treating this form we now believe a two or three months' therapeutic trial with sulfanilamide, as well as other forms of medical management, closely checked by progress proctoscopic examinations (regardless of relief or continuance of symptoms), is indicated before considering surgical procedures, unless contraindications to the use of the drug or obvious complications which demand

surgical intervention exist. The extensive work done by Bargen[1] has resulted in immeasurable clarification of many aspects of this disease, including the definite indications for surgical intervention.

The incidence of chronic ulcerative colitis is increasing, probably due to the more frequent use of stool, proctoscopic, and roentgen examinations of the colon. Universal acceptance of a single etiologic agent has not been established. Sulfanilamide has been employed with excellent results in the treatment of so many types of infectious processes that its use in the treatment of this disease was only a matter of course.

In reporting the results secured from any form of management of this disease, we believe certain criteria and classifications should be used, such as those suggested by Kiefer[2], namely, Group 1, the nontoxic, nonsclerotic group of cases; Group 2, the nontoxic, sclerotic group; and Group 3, the toxic group wherein fever, nausea, vomiting, rapid pulse and prostration, as well as leukocytosis, are present. The mortality rate and the surgical indications are, of course, greatest in the third group. The chief characteristic of the disease is its variable severity. Kiefer has emphasized the fact that its variable severity is probably most important in determining the final outcome of an individual case, and is probably more important than the apparent extent of the disease as determined by roentgen examination. When treating patients belonging to the first two groups, more time may reasonably be allowed for medical management before considering the use of surgical procedures than is the case when dealing with patients belonging to the third group.

Case Reports

Case 1: (Nontoxic, nonsclerotic). A man, 27 years of age, entered the clinic complaining of recurring attacks of lower abdominal cramps, tenesmus, and four to ten loose stools daily, occasionally containing blood. These symptoms had been present for ten years. Each attack varied in duration from several days to several weeks, and recurred at least twice a year with complete remission of symptoms between attacks. There was no history of chills and fever and there was no loss in weight.

The findings on stool and proctoscopic examinations were characteristic of chronic ulcerative colitis; in fact, Dr. Thomas E. Jones reported the proctoscopic findings as showing the late stage of the disease. The roentgen examination of the colon revealed normal findings except spasticity of the left colon. Sulfanilamide, 45 grains daily, was given by mouth, and since repeated studies of the blood did not show any findings which would contraindicate the use of the drug, it was continued for two months. Proctoscopic examination at this time was reported as showing "practically a normal rectal mucosa; bleeds only on very rough swabbing." There was complete remission of symptoms which started on the tenth day of treatment and has continued to and at the end of one year. After the sulfanilamide was discontinued, small retention enemas of colloidal aluminum hydroxide and kaolin[3] were used three times weekly for two

months. The proctoscopic findings were then entirely normal and have remained so up to the time of this report, one year after starting sulfanilamide therapy.

Although there was a history of symptoms for ten years, there was apparently a relatively low degree of severity of the process. The patient remained ambulatory and the disease did not interfere with his occupation.

Case 2: (Nontoxic, nonsclerotic). A man, age 39, had symptoms and objective findings similar to those mentioned in Case 1, except that, five years prior to entrance, the symptoms had been present for two months, followed by a remission which lasted until four weeks preceding our examination in March, 1936. During these four weeks the patient stated that he had "innumerable stools" containing blood, as often as every 20 minutes during the daytime and every half hour during the night hours. He "lived in the bathroom." There was no history of chills and fever, and he had lost only five pounds in weight. He was unable to work and an anti-amebic therapeutic test, extending over several weeks, resulted in no improvement. On April 6, 1936, the subcutaneous use of an autogenous vaccine was started. On May 16, 1936, after having had daily administrations of the vaccine, the symptoms were somewhat relieved and the patient was not seen again until October 25, 1937. At this time he stated that he had been well until two weeks prior to re-entrance, but during the two weeks "all of the former trouble has recurred." Proctoscopic examination revealed extensive, acute involvement of the rectal and lower sigmoid mucosa, and roentgen examination showed extension of the disease to the mid-descending colon. Sulfanilamide (in the dosage mentioned in Case 1) was started October 27, 1937, at which time the patient was having at least 20 stools in 24 hours, many of which contained blood. Twelve days later he was having not more than four stools in 24 hours and felt "excellent"; four days later he was having only one stool in 24 hours and he returned to work. After he had had 45 grains of sulfanilamide daily for 44 days the proctoscopic findings were practically normal. There were no ulcers and no bleeding on rough swabbing. On December 24, 1937, when the sulfanilamide was stopped, he was having no abdominal distress, was on a full diet, and was having not more than two formed stools daily. This, as well as normal proctoscopic findings, have continued to approximately the date of this publication.

This case is quoted to show the difference in the time element of response to treatment to sulfanilamide therapy as compared with that of autogenous vaccine, all other factors remaining approximately the same.

Case 3: (Mildly toxic). A housewife, 42 years of age, had had recurring attacks of diarrhea, "20 or more stools, often containing blood, in 24 hours," during the preceding six years. Fever had been present and the patient was bedridden during several of the attacks. One attack had lasted six months and another 16 months. Proctoscopic examinations during these times were always reported as showing "typical chronic ulcerative colitis." Two years prior to entrance she had a skin eruption and a diagnosis of dermatitis herpetiformis was made. Allergic investigation was instituted and the eliminaton of allergens as determined by skin tests resulted not only in the relief of the skin trouble but also some improvement in the symptoms due to the colitis. Extensive treatment with autogenous vaccines apparently had had no permanently beneficial effect.

Proctoscopic examination at the time of admittance revealed an extensive process involving the entire rectal mucosa. Roentgen examination of the colon did not show evidence of abnormality above the sigmoid colon. During the following three months the patient used aluminum hydroxide and kaolin retention enemas daily during the first month and approximately three times weekly thereafter with complete relief of symptoms, but the proctoscopic findings at the end of this time were practically the same as observed at the time of admittance.

The use of sulfanilamide was started in December, 1937, and the dose, by mouth, did not exceed 45 grains daily. The patient remained ambulatory throughout the course of treatment. Twenty-four days later, chills and a fever ranging between 102 and 104° F. developed. These were attributable to nothing other than the use of the drug and three days after its discontinuance the temperature returned to normal. Since that time the patient has had only one or two formed stools daily and has not observed blood or pus. Much to our surprise, proctoscopic examination on February 9, 1938, revealed considerable improvement, and a recheck examination on March 25, three months after sulfanilamide was used, revealed normal findings except for a small granular area about one inch proximal to the anus.

Since this patient gave a history of fever and severe prostration during several of the exacerbations of symptoms, her case has been included in the Group 3 or toxic group. Although many forms of treatment had been used during six years, including management from the standpoint of allergy as determined by skin tests, the use of autogenous vaccines and the use of aluminum hydroxide and kaolin retention enemas (three months), to our knowledge, proctoscopic findings had never shown improvement until sulfanilamide was used.

Case 4: (Severely toxic.) A housewife, 51 years of age, was admitted directly to the hospital in an acute fulminating attack of ulcerative colitis. During the preceding 10 days she had had countless stools night and day with continual tenesmus. The temperature varied between 100 and 102° F. during the first week in the hospital. The stools contained much pus, blood, and mucus. The proctoscopic examination revealed the presence of an acute ulcerative colitis as far as the scope could be passed. The roentgen examination, using the barium enema, revealed evidence of typical infiltration characteristic of a diffuse ulcerative colitis from the rectum to the hepatic flexure of the colon. She had lost 30 pounds in weight during the previous three months, due in part to a marked anorexia and vomiting at irregular intervals, as much as four times daily. The exact duration of the disease could not be determined. Although the diarrhea had been of relatively short duration she had not been well for eight months because of malaise and anorexia.

The patient was in the hospital approximately one month and during this time received five blood transfusions, parenteral liver extract, and vitamin B_1. Due to the lack of free hydrochloric acid in aspirated test meals, 1 drachm of dilute hydrochloric acid was given constantly with each meal as soon as she was able to tolerate food by mouth.

Sulfanilamide and soda bicarbonate, of each 40 grains daily, were given for 20 days. Within two weeks from the time these medications were started, the temperature became normal, appetite and gain in weight were restored, no more than two stools in 24 hours were passed, and these factors remained the same

during the remainder of the hospital sojourn. Aluminum hydroxide and kaolin retention enemas were used during the final two weeks, at the end of which time there was marked improvement in the proctoscopic findings.

Four months later she reported that her general condition had remained excellent. She had been entirely free from symptoms since leaving the hospital and had gained 23 pounds in weight. The aluminum hydroxide and kaolin retention enemas had been used twice weekly for two months but during the two months prior to re-entrance she had not used these or any other type of medication. The stools, proctoscopic, and blood findings were entirely normal.

This case report is given as an example of an acute fulminating toxic type of ulcerative colitis, the type which may prove fatal. The response to therapy to date has been unusually gratifying.

Another group of four cases responded similarly to the use of sulfanilamide therapy. Two of these are classified as belonging to the nontoxic, nonsclerotic group and did not present evidence of extension of the disease above the lower sigmoid colon. The other two cases are included in the severely toxic group and there was roentgen evidence of involvement of the entire colon in both instances. Additional details pertaining to each of these four cases are not presented because of the similarity to those quoted, according to the classified grouping in each instance, in the first four case reports.

There was no response to sulfanilamide therapy in three cases. These belonged to the severely toxic group and there was extensive involvement of the colon in each instance. Other forms of medical management have proved effective to date, so that no surgical procedure has been used in the eleven cases selected for this investigation.

Summary of Results

Sulfanilamide therapy was used in the treatment of chronic ulcerative colitis in eleven cases. An unusually rapid and satisfactory initial response, which has been maintained to the date of publication, was obtained in eight of the eleven cases. In those in whom the use of the drug proved effective, the results were unusual because we have not seen a similar response while using other forms of medical therapy in similar conditions. Of the eight cases wherein a favorable response was obtained, four were ambulatory patients, belonging to the nontoxic, nonsclerotic group in whom there was no evidence of extension of the disease above the sigmoid colon except in one instance where there was involvement up to the mid-descending colon. The other four were toxic cases, one was mildly toxic and did not have evidence of involvement above the sigmoid colon, while three were severely toxic and were admitted directly to the hospital in the acute fulminating stage of the disease, with involvement of the colon up to the hepatic flexure in one case and involvement of the entire colon in two cases.

Sulfanilamide therapy was not effective in three severely toxic cases, in each of which there was extensive involvement of the colon.

Comment

Final appraisal of the use of this drug must, of course, await the "follow-up" repeated stool, proctoscopic, and roentgen examinations of the rectum and colon, extending over years of time, as well as the continued relief of symptoms. At the time of the initial examination, we believe the physician should spend more time than is customary in acquainting the patient with the characteristics of the disease. The patient must understand that a remission of symptoms does not signify a "cure," and that the only criterion of value, so far as the likelihood of his not having additional acute exacerbations of the disease is concerned, can be established only by making the progress examinations mentioned.

At the time of the initial examination, regardless of whether there is evidence of amebiasis on stool and proctoscopic examinations, we commonly place the patient on a therapeutic test, using anti-amebic therapy. Only in this way do we conclude that the Endameba histolytica is not the etiologic agent.

Our next step in therapy, at the present time, is a therapeutic trial with sulfanilamide. If the drug is well tolerated we believe its use should be continued for two or more months in relatively low dosage before deciding that it is ineffective. Recently, we have given sulfanilamide by rectum on alternate weeks in certain individuals, with satisfactory initial results.

In the ambulatory patients belonging to the nontoxic, nonsclerotic group of cases, we have made progress proctoscopic examinations while the patients were receiving only sulfanilamide therapy and an intestinal low-residue, high-vitamin diet. The patients in this group were able to resume their usual occupations after receiving sulfanilamide for 16 days or less.

In the severely toxic group in which the patients were admitted directly to the hospital in the acute fulminating stage of the disease, repeated blood transfusions, parenteral administration of vitamins, and other measures heretofore commonly used in this group of cases, aside from the use of sera and vaccines, were utilized. These features were considered on a comparative basis in the appraisal of the initial response to sulfanilamide therapy.

Clinicians who are particularly interested in treating this serious and disabling disease know that any therapeutic procedure which has shown promise of relieving the patient's disability must be given

adequate trial. Too often no change is noted in progress examinations, regardless of the complete remission of symptoms. Therefore, the clinician commonly uses several types of treatment concomitantly or in sequence, and in the end has difficulty in the final appraisal of any one procedure. This applies particularly to the severely toxic cases in which the mortality rate is the highest. Since the use of sulfanilamide is a new procedure, we have discontinued this form of therapy as soon as we considered it had been given an adequate trial. In many instances in both groups quoted, aluminum hydroxide and kaolin retention enemas have been used during the *convalescent* stage after a favorable response to sulfanilamide therapy has been shown by proctoscopic examination as well as a remission of symptoms. The preparation used at first was that described by Eyerly and Breuhaus[3], but due to the occasional occurrence of hard stools this was discontinued in favor of a similar preparation to which mineral oil had been added, as advocated by Fradkin[4]. At present we are using two ounces of this preparation* diluted with two ounces of distilled water or larger quantities, depending upon the extent of the disease, every one to three days during the convalescent stage of the disease as determined by progress proctoscopic examinations. The use of this preparation during the acute phase has not proved as effective as sulfanilamide in our experience.

Disadvantages to the Use of Sulfanilamide

The possible toxic effects resulting from the use of sulfanilamide have been emphasized in many papers published in the Journal of the American Medical Association during the past year. In two of our patients a high fever developed between the tenth and twenty-fourth day of its administration. In these instances, no deleterious effect has been observed since its immediate discontinuance. A common observation has been that patients belonging to the severely toxic group have pallor or cyanosis during its administration, but this has not been found to be a contraindication to its use. However, the patient's relatives and friends should be warned of this possibility before the drug is started. In every instance, repeated studies of the blood have been made and the most common finding has been a lowering of the hemoglobin content of the red blood cells. Blood transfusions in the toxic cases and adequate administration of iron products in the nontoxic cases, during the intervals when sulfanilamide was not used, have counteracted this tendency in our more recent experience. Since sulfanilamide is eliminated in the urinary tract, we now believe tests of renal function, including the urea clearance test, should be done before considering

* Now available on the market as Kaomagma, Rectal, John Wyeth & Brother, Inc., Philadelphia.

this mode of therapy. The value of a high fluid intake to aid in kidney excretion has been demonstrated in cases showing evidence of toxicity to the drug. In certain instances, the toxic effects varied according to the method used in the administration of the drug.

Mode of Administration

At first sulfanilamide was given orally in nontoxic cases and parenterally in severely toxic cases at the start of the treatment. An attempt was made to maintain a blood level between 8 and 10 mg. per 100 cc. of blood. Toxic effects were quite commonly observed and we learned to use this drug with caution. General malaise, headache, anorexia, nausea, and increased diarrhea occurred and patients were forewarned of this possibility. On the other hand, we believed that unless a relatively high concentration in the blood was maintained the drug was not being given an adequate therapeutic trial. Skin manifestations were not uncommon. We were searching for an adequate blood sulfanilamide level which could be maintained over a relatively long period of time, longer than had been the custom with its use for other types of infections.

More recently we have found that the administration of the drug by retention enema has not been so commonly associated with the toxic effects mentioned, that adequate absorption occurs as determined by blood sulfanilamide determinations, and that although the blood level is lower than mentioned above, equally effective results have been obtained as shown by progress proctoscopic examinations, aside from the relief of symptoms. In the severely toxic cases and in patients having many loose stools per day, opium suppositories have been used before the rectal administration and small quantities were given at a time at the start of treatment. With clinical improvement, larger quantities were retained until one or two retention enemas fulfilled the usual routine 24 hour dosage of not more than a total of 45 grains (powder form) in one pint of distilled water, warmed to body temperature. In our experience to date this dosage has resulted in maintaining a blood sulfanilamide level of 5 to 7 mg. per 100 cc. of blood in most instances, but the degree of absorption of course depends on the severity and extent of the diseased process.

Because of the tendency to the production of a hypochromic anemia while using sulfanilamide, which we have observed when the drug has been used over several months of time and no other toxic effects were demonstrable, we now commonly give the drug by retention enema intermittently, with high iron therapy in the intervals. The incompatibilities of sulfanilamide with other drugs, particularly the sulphates, is now well recognized.

Sulfanilamide is not a harmless drug to be dispensed without supervision by a physician. Obvious surgical indications must be excluded before this form of therapy is considered. Individual tolerance to the drug must be determined by clinical observation and repeated blood counts. On the other hand, to be effective, repeated blood sulfanilamide determinations should be made in order to determine the correct dose for each patient and to make certain that adequate absorption is maintained during certain periods of time, as checked by proctoscopic examinations. As in diabetes and other chronic disorders these criteria can be established to best advantage by observation in a hospital at the start of the treatment. Too much emphasis cannot be placed on these factors because of the seriousness of the disease and the disability associated therewith, the long duration of the treatment at the patient's home, and the need for progress stool, proctoscopic, and roentgen examinations, regardless of the remission of symptoms, in order to appraise this form of therapy.

Conclusion

In view of our experience with 11 cases of chronic ulcerative colitis during the past year, in which a favorable initial response to sulfanilamide has been observed in eight cases, we believe this form of therapy should have a more thorough trial.

The difficulties in the appraisal of any single form of therapy in this serious disease have been emphasized.

Unless surgical indications are present at the time of the initial examination, we believe an adequate therapeutic trial with sulfanilamide should be included in the medical management of this disease, provided no contraindications to its use exist.

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THE PARAFFIN BATH

WALTER J. ZEITER, M. D.

The paraffin bath affords a simple and efficient method for applying heat to the surfaces of the body, especially to the hands and feet. During the World War, Dr. James A. Dickson of our Orthopedic Department had an extensive experience in the use of paraffin in injuries of the extremities. He used a bath which was enclosed with a water jacket and heated with gas. The results from this type of equipment were so gratifying that an electrically controlled bath which we now use was developed. These baths are available for hospital, office and home use (Figs. 1 and 2). The inside of such a bath is constructed of stainless metal, and the outside casing is of chrome plated steel. Built in are the melting and maintenance elements which are insulated with firmly packed mineral wool. Slats of bakelite or wood fastened to strips of stainless metal are placed on the bottom of the bath to protect the patient's extremities from touching the heated metal. The melting and maintenance elements are controlled by thermostatic time switches. If the paraffin is congealed, the melting element is used until the paraffin is nearly at the operating temperature, then the maintenance element, independent of the melting element, keeps the bath at that temperature.

Ordinary commercial paraffin is used. This may be obtained at different melting temperatures which range from 123° to 136° F. By the addition of paraffin oil the melting point can readily be controlled. Our baths are operated at a temperature of about 126° F.

Before immersing the extremity to be treated, it is bathed and carefully dried. Then the patient dips the member in and out of the bath quickly, so that a thin coating of paraffin congeals on the skin. This process is repeated several times until the glove of the paraffin is of sufficient thickness to allow the part to remain in the bath with comfort. The patient keeps the extremity immersed in the bath for from ten minutes to half an hour. Then the glove of adherent paraffin is removed and replaced in the bath, following which massage and reeducation of the muscles are instituted. The skin always remains soft, pliable, and moist when this procedure is employed; it is not withered and shriveled as it is from contact with water. Characteristic hyperemia results (Fig. 3).

Quite frequently the paraffin bath can be used to great advantage in the home. For this purpose we have used a double boiler very successfully (Fig. 4), giving the patient the following instructions:

Hands: Fill the top of a large double boiler (6 quart) with paraffin

FIGURE 1: Paraffin bath for hand and arm.

(6 to 8 pounds) and the lower part with hot water. Heat until almost all the paraffin is melted but be sure an unmelted piece remains. This is important if burns are to be avoided. Remove from fire, leaving water in bottom of boiler.

Dip hand quickly into paraffin, keeping the fingers separated and being

FIGURE 2: Paraffin bath for feet.

careful not to touch the sides or bottom of boiler. Remove hand from boiler until paraffin hardens, then dip and quickly remove again. Repeat this procedure until a thick glove is formed, and then keep immersed in the paraffin for from ten minutes to half an hour. Peel off glove and put paraffin back into boiler (Fig. 3).

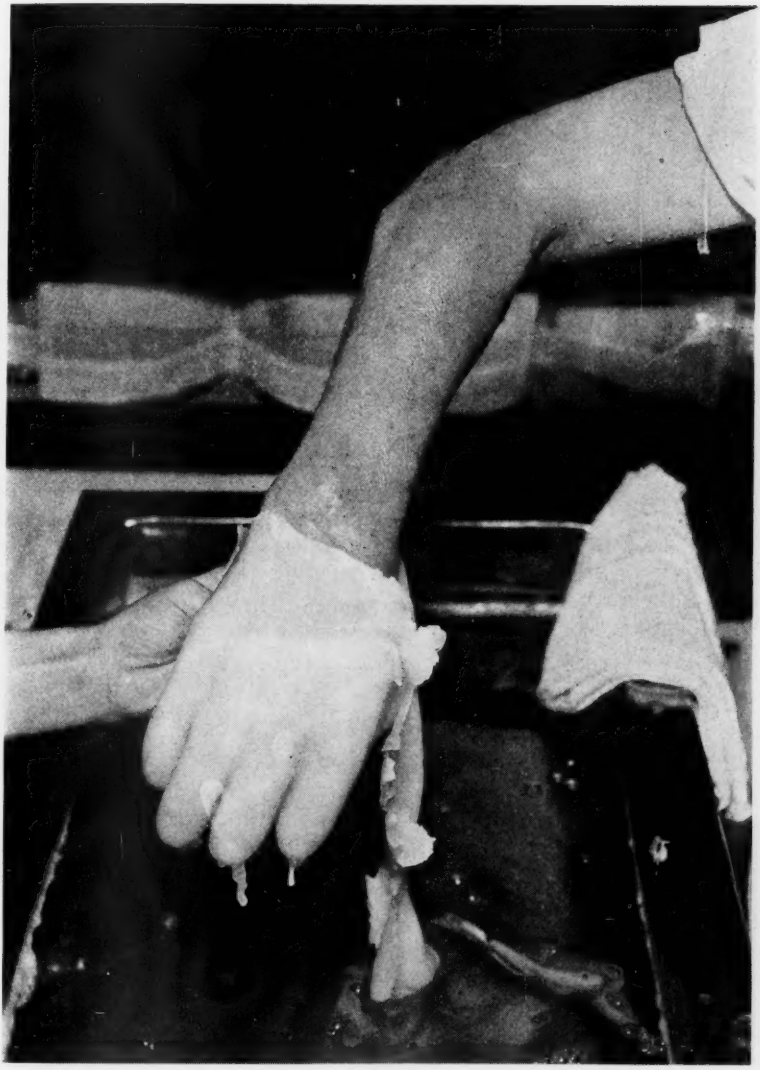

FIGURE 3: Removal of paraffin glove after treatment, showing typical hyperemia.

If exercise is prescribed, squeeze and mold piece of warm paraffin in the hand before putting back in boiler.

It is well to have a thermometer to check the temperature of the paraffin; however, this is not essential as will be noted from the above directions. If an unmelted piece of paraffin remains or if the paraffin

FIGURE 4: Double boiler for home treatment of hand and wrist.

is allowed to cool until it begins to congeal on the surface it will be perfectly safe to use.

When other forms of heat are not available for treating different parts of the body, paraffin can be applied in a simple manner. After it is melted, a clean, warmed paint brush is immersed and the part to

be treated is painted rapidly with about a dozen coats of liquid paraffin. When the paraffin is first applied to the skin, it will feel very warm. This thick coating which retains its own heat for a considerable period of time is allowed to remain on the area for twenty to thirty minutes. This simple method, too, can readily be made available in every household.

The paraffin bath is particularly indicated in the treatment of arthritis because of the ease and simplicity with which it may be applied. It is also effective in the presence of stiffness of joints following lacerations or infections, in the treatment of scars restricting motion of joints and tendons, in involvements of joints secondary to lesions of nerves, in sprains, and in contusions. In other conditions, such as fibrositis of lumbar area, it can be applied with a paint brush as described above.

Because of the marked heat, the paraffin bath must be used judiciously in old, weak, and debilitated individuals. If circulatory and sensory changes are present, the application of paraffin should be done cautiously because of the danger of burns. Open wounds, cuts, and skin infections are better treated by other methods. If the ordinary precautions mentioned previously are taken, burns will be avoided. Repeated use of the paraffin locally in some patients may rarely produce a mild erythema ab igne.

The paraffin bath is believed by some to be less sanitary than other procedures. There is, however, no basis for this belief, since the bath, as well as the double boiler used for home purposes, can be readily sterilized.

With the ordinary precaution of cleaning out the tank, using new paraffin, and insisting that each patient be bathed before entering the bath, this objection is negligible.

The paraffin bath affords a simple method of applying heat to various parts of the body, especially to the hands and feet. It is simple to operate and maintain, and the upkeep cost is low. With proper instructions, it affords a simple method for home use when other means are not available.

CHOKED DISCS ASSOCIATED WITH OTITIS MEDIA

An Explanation of the Mechanism in Certain Cases

W. JAMES GARDNER, M. D.

Otologists are occasionally confronted with the problem in which the patient, making an apparently uncomplicated convalescence from an attack of otitis media, is found to have a choking of the optic discs. Because other symptoms of increased intracranial pressure are lacking, the condition may be called an optic neuritis. Spinal puncture in these cases, however, will usually disclose a high degree of intracranial pressure with no increase in the cell count of the spinal fluid.

In 1896, Quincke[1] described a syndrome in which the signs of increased intracranial pressure were associated with the findings of clear cerebrospinal fluid on lumbar puncture. He called attention to its occurrence chiefly in young women and its association with ear infections, head injuries, and other factors. He believed that, in these cases, there was an excess of cerebrospinal fluid as a result of hypersecretion of the choroid plexus. He referred to the condition as serous meningitis.

Numerous terms have since been used to describe and label these cases. In the group in which an otitic infection apparently initiated the syndrome, different authors have supplied the name cerebral pseudoabscess, meningismus, serous meningitis, serous ependymitis, arachnoiditis, hypertensive meningeal hydrops, toxic hydrocephalus, and otitic hydrocephalus.

During the past eight years, 23 patients have come to the Clinic presenting a high degree of intracranial pressure, the cause of which could not be adequately explained. Of these 23 cases an otitic infection initiated the syndrome in 10 instances. This high incidence of otitic infection naturally suggests that these cases constitute a disease entity with a common etiological factor related to the otitis.

In 1931, Symonds[2] published an article in which he applied the term otitic hydrocephalus to the syndrome of increased intracranial pressure following an ear infection. He believed that the condition was due to an increased amount of cerebrospinal fluid. In a more recent article[3], he concludes that in this syndrome infection of the lateral sinus is the most important etiological factor, but that *obstruction* of the sinus is not an essential factor. He suggests that mural thrombophlebitis of the superior longitudinal sinus, by retrograde extension from the lateral sinus, may, by putting out of action a sufficiently large proportion of the arachnoid villi, so interfere with cerebrospinal fluid absorption as to cause otitic hydrocephalus.

A study of the ten cases we have observed also indicates that the

syndrome is due to sinus thrombosis. However, encephalograms which were made in ten cases will not permit of a diagnosis of hydrocephalus. It would appear rather that the increased intracranial pressure is due to venous congestion occasioned by interference with the venous outflow from the cranial cavity. The case which suggested sinus thrombosis as the cause of the increased intracranial pressure in this group was observed in 1934.

Case 1: This patient was a girl of nine years whose history stated that two years previously a discharging left ear had suddenly developed without previous pain. The discharge ceased after a few days and there appeared to be no sequelae. However, about one month later, while on a visit to another city, it was found that the vision was seriously impaired due to a marked choking of the optic discs. A right subtemporal decompression was performed, the choking of the optic discs subsided, and the vision returned. The patient had been in good health since that time, but there was a constant bulging at the site of the decompression, although this hernia was not tense.

Three days prior to her entry on January 20, 1934, a second attack of left otitis media developed. At the time of admission her temperature was 105° F. and she appeared quite ill. During the next few days there was a marked diurnal fluctuation in the temperature, and on the seventh day of her illness a left mastoidectomy was performed, disclosing a large amount of pus in the mastoid. A perisinus abscess was present and it was noted that the sinus was white in color instead of the usual deep blue. Culture revealed a type III pneumococcus. The temperature continued to fluctuate and on the twenty-first day of the illness the left internal jugular vein was ligated. The temperature subsided somewhat after this, but the hernia became quite tense and choking of the optic discs began to appear. The spinal fluid pressure was found to be 400 mm. of water. The fluid contained 110 cells, 60 per cent of which were lymphocytes and 40 per cent polymorphonuclears. After this, a definite purulent meningitis developed from which a type III pneumococcus was cultured and the patient died on the thirty-fourth day.

At postmortem examination the left lateral sinus was found to be represented merely by a fibrous cord, indicating that there had apparently occurred a thrombosis of this sinus with the attack of symptomless otitis two years previously, and that this thrombosis, which had healed without suppuration, had been the cause of the increased intracranial pressure at that time. There was an acute thrombophlebitis of the left superior petrosal sinus and of the sagittal sinus, together with an acute, diffuse fibrinopurulent leptomeningitis.

COMMENT: This, then, is a case of "Otitic Hydrocephalus" with recovery following the first attack and with necropsy findings after the second attack. This led to the belief that the condition which Symonds had described in 1931 under this title might be due to thrombosis of the intracranial sinuses which, by partially obstructing the venous outflow from the cranial cavity, causes an increased intracranial venous pressure, cerebral venous engorgement, and a consequent rise in intracranial pressure. Otologists have long been aware that papilledema occurs in a considerable percentage of cases of sinus thrombosis com-

plicating otitis media but Symonds, in 1937[3], was the first to offer convincing proof that the syndrome under discussion is due to sinus thrombosis.

Sinus thrombosis may be asymptomatic and may occur in the course of a very mild otitis media—a fact which is not universally recognized. Also, if secondary infection does not occur the thrombus will heal without suppuration and usually with recanalization. As recently stated by Sutherland[4], "A thrombus is essentially a protective measure and is not, as the minority believe, infected from the beginning. It is nature's method of blocking the blood channel in an effort to prevent further spreading of an infection. It is the secondary infection of the clot and not the thrombus that constitutes the danger."

In addition to this case, nine other cases have been observed. In seven of the ten cases the ages were between seven and twelve years. Sinus thrombosis was proved at autopsy or at mastoidectomy in five cases and its presence was indicated by the Toby-Ayer test in three additional cases. In one case a perisinus abscess was found but the lateral sinus bled when incised. In the remaining case there was no definite proof of sinus thrombosis. Encephalograms in six cases showed no evidence of an expanding lesion or of hydrocephalus. The total volume of the cerebrospinal fluid was increased in only one instance. All patients were treated by repeated spinal punctures with the exception of one case in which the pressure was only 200 mm. of water and the process was subsiding spontaneously. In four cases subtemporal decompression was performed. The intracranial pressure returned to normal in from one to eleven months in seven cases. In one case the pressure is still present three and one-half months after the onset. Two cases which came to necropsy showed extensive thrombosis of the dural sinuses, including the longitudinal sinus. In seven instances the disease process was on the right side and in three on the left side.

In Symonds' experience also this syndrome was found more frequently after a right otitis media. The explanation of this is found in the anatomy of the dural sinuses. When one of the lateral sinuses receives most or all of the blood from the superior longitudinal sinus, it is more liable to be the right than the left. Therefore, a thrombus of the right lateral sinus is more apt to seriously impair venous return from the cranial cavity and is also more apt to extend into the longitudinal sinus than is a thrombus in the left lateral sinus. On purely anatomical grounds, Symonds estimated that the chances of a right as opposed to a left lateral sinus thrombosis extending into the superior longitudinal sinus are as about 6 to 4 or 7 to 3. Of 26 cases of this disease, including his own, the right ear was affected in 17 and the left ear in 9. Adding

my cases there are now 24 cases following right otitis media and 12 after left otitis media.

Discussion

I should like to call attention to some false interpretations of certain observations which have been made in these cases. First of all, the fact that one can obtain a large amount of cerebrospinal fluid at lumbar puncture before the pressure is reduced to normal does not mean that an increased amount of cerebrospinal fluid is present. Due to the obstruction of the venous outflow in these cases, as spinal fluid is removed, it is immediately replaced by an increased amount of venous blood within the already engorged cerebral veins. This cerebral venous engorgement forces a larger quantity of cerebrospinal fluid out of the lumbar puncture needle than one would be able to obtain if the venous obstruction were not present. Everyone is familiar with the fact that a larger quantity of fluid can be obtained at spinal puncture if one applies jugular compression to increase the pressure and the rate of flow. A similar factor is operative in these cases. In other words, the effects of sinus thrombosis may be compared to the effects of continued jugular compression.

Another frequent observation in this type of case is that when a trephine is performed, the arachnoid membrane is found to be distended with fluid. This observation has led the surgeon to assume that an external hydrocephalus is present. This, however, is not the case, at least not in the majority of instances. Since the encephalographic films in these cases give essentially negative findings, it seems fair to assume that the distention of the subarachnoid space as disclosed at trephine is due to the local accumulation of fluid in the subarachnoid space at the site of operation due to the release of pressure at this area. In other words, in these cases there is a normal amount of cerebrospinal fluid which circulates freely so that when the increased pressure is released at a localized area, as in a decompression, the fluid rapidly flows to that point, causing a local distention of the subarachnoid spaces.

Still a third observation in these cases which has led to the belief that hydrocephalus is present is the fact that occasionally when a cannula is introduced into the lateral ventricle, there occurs a copious flow of fluid. This has been interpreted as meaning that the ventricles are dilated. That this assumption is incorrect is shown by the fact that in these cases the ventricles are normal in size or even smaller than normal, as demonstrated by encephalography. When one can obtain a large quantity of fluid from the ventricle in a case of this sort it simply means that, due to the absence of obstruction in the cerebrospinal fluid system, the expanding intracranial veins squeeze all the fluid toward the

point of exit. Therefore, toward the end of the drainage the fluid that is escaping from the cannula is really subarachnoid fluid which has been forced into the ventricle as a result of the drainage. In these cases, one cannot estimate the size of the ventricles from the amount of fluid obtained by ventricular puncture.

In conclusion, therefore, I am in entire agreement with Symonds that the syndrome of increased intracranial pressure without localizing signs occurring after an attack of otitis media is usually due to intracranial sinus thrombosis; that when this picture of increased intracranial pressure is associated with localizing cerebral signs and recovery occurs without suppuration, it means that the thrombus (probably sterile) within the intracranial sinuses has extended into the cerebral veins. I am not convinced, however, that the thrombus must necessarily extend into the sagittal sinus in order to produce increased intracranial pressure. If, as is not infrequently the case, one of the lateral sinuses constitutes the chief emissary for the intracranial circulation, then I believe that it is possible for a thrombosis of this sinus alone to produce the picture of increased intracranial pressure. Since the total volume of the intracranial fluid is usually not increased and since the encephalograms in these cases gave essentially normal findings, there obviously is no hydrocephalus. I am inclined to attribute the increased intracranial pressure simply to an engorgement of the intracranial veins plus, in some cases at least, the occurrence of a sterile subdural effusion as the result of external pachymeningitis. Recovery from this state of increased intracranial pressure occurs when, by means of recanalization or the development of collateral supply, the venous return from the cranial cavity is once more adequate. The chief value of a subtemporal decompression in these cases is not that it causes a satisfactory reduction of the intracranial pressure but that the degree of tension in the hernia serves as a guide as to when a therapeutic lumbar puncture should be done. An adequate name for this syndrome is "sinus thrombosis causing intracranial pressure."

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THE TREATMENT OF EXTRASYSTOLES

A. Carlton Ernstene, M.D.

Premature beats usually are of no clinical importance and seldom require treatment. Although they occur in many patients with organic heart disease, they are much more common in individuals with perfectly normal hearts and can never be interpreted as evidence of heart disease. Often they cause no symptoms even though they occur at frequent intervals. Certain individuals, however, and particularly those who are hypersensitive may complain of distinctly disagreeable sensations which result either from the premature beat itself or from the forceful systole which follows a long compensatory pause. Among the most common of these symptoms are an awareness of a pause in the heart's action followed by a sudden, forcible pulsation, a sensation of choking or fulness in the throat, a feeling that "the heart has suddenly risen into the throat," or momentary light-headedness. Other patients state that the heart seems to turn over in the chest, and an occasional person complains of sharp, sticking pain in the precordium. Symptoms such as these often cause great apprehension.

Frequently, no cause can be found for premature beats. There are, however, a number of factors which at times appear to be directly responsible, and it is advisable to investigate these possibilities in all cases, since their detection and correction may result in prompt disappearance of the irregularity. The most common causative factors are excessive nervous strain, excitement, fatigue, infectious diseases such as pneumonia, influenza, meningitis, and acute tonsillitis, chronic constipation, and individual susceptibility to tobacco, coffee, tea, and alcohol. Organic heart disease, either with or without congestive heart failure, appears to be directly responsible at times, and occasionally there is an apparent relationship to focal infection about the teeth or in the tonsils or nasal sinuses. Although physical activity usually causes the irregularity to diminish or disappear, exertion is the most important precipitating cause in certain patients. Occasionally, one encounters very unusual relationships as in the case of a patient who could invariably induce frequent premature beats by eating a small amount of chocolate candy. Digitalis will cause extrasystoles whenever given in sufficient amounts.

A thorough history and physical examination are essential in the study of patients who have premature beats. Careful inquiry should be made concerning the customary mode of living, the average consumption of tea, coffee, alcohol, and tobacco, the hours of work and the stress and strain incident to the occupation, the presence of family or financial worries, the opportunities for recreation, the amount of sleep obtained,

the bowel habits, and the presence of other symptoms referable to the cardiovascular system. In the individual who is using coffee, tea, tobacco, or alcohol to excess, the giving up of these substances or even a reduction to a more nearly normal level may result in prompt disappearance of the arrhythmia. When worry and nervous strain are the apparent causes, the administration of mild sedatives and the institution of a simple program of recreation often prove very helpful. If physical fatigue appears to be a significant factor, the hours of sleep should be regulated and, whenever possible, a rest period after lunch should be arranged. It is important to remember that refractive errors and eye muscle imbalance may play a prominent rôle in the production of mental and physical fatigue. When constipation is present, appropriate dietary measures should be prescribed and an effort should be made to establish a regular habit-time for defecation.

In the physical examination, particular attention should be paid to evidence of focal infection and to the signs of organic heart disease. Caution must be exercised, however, in the matter of focal infection, for altogether too often the eradication of obvious foci fails to have the least influence on the premature beats. Premature beats occur at times in patients with organic heart disease but they are of no significance in prognosis. The onset of congestive heart failure may be responsible for an increase in their number or even for their initial appearance, and in such cases treatment by rest in bed and the administration of digitalis may result in their disappearance or a decrease in their frequency.

The development of premature beats during an acute infectious disease should not be a cause for concern. The cardiac rhythm becomes normal during convalescence and no special therapeutic measures are necessary.

In many individuals a careful history and physical examination fail to reveal a cause for the occurrence of extrasystoles. If the arrhythmia is not causing symptoms, no treatment is necessary. If symptoms are being experienced or if the patient has become apprehensive after chance discovery of the irregularity, reassurance that the condition is not due to organic heart disease and is of no importance may be all that is required. If this does not suffice, symptomatic measures may be employed. Simple sedatives such as the bromides or phenobarbital may be given in suitable doses two or three times a day and are often very effective. In the event that they do not give relief, one may administer quinidine sulphate in doses of three grains (0.2 gm.) two or three times a day. Numerous other preparations have been suggested from time to time, but it has been our experience that, if the sedatives and quinidine sulphate fail, nothing else will prove of value.

In conclusion, whenever premature beats of which the patient is not aware are discovered during a physical examination, the individual should be told of their presence and should be fully instructed about their lack of importance. This course will serve to prevent the apprehension that might arise in the event of their later detection by the patient or by someone with limited knowledge of their clinical significance.

THE INTERPRETATION OF QUALITATIVE CHANGES IN NEUTROPHILIC LEUKOCYTES

"Shift to Left"—"Shift to Right"—"Toxic" Granulation

RUSSELL L. HADEN, M. D.

The neutrophilic granulocyte (polymorphonuclear neutrophilic leukocyte) plays a major rôle in the mechanism of defense against infection and toxemia. The defensive value of this cell depends upon its maturity and the integrity of its chemical substances which normally enable it to dispose of bacteria and poisons. The quality of the neutrophilic granulocyte is thus even more important than the quantity.

The granulocyte is essentially a drop of protoplasm containing active ferments surrounded by a membrane. Anything interfering with the development of the protective substances or injuring them must impair the usefulness of the cell. All granulocytes are formed in the bone marrow. Each cell goes through a definite cycle of development and maturation before entering the circulation. When a granulocyte is released from the marrow, its development normally is complete. No further changes take place while it is in the circulation or tissues except those incidental to the death of the cell.

The granulocytes have no function in the blood stream. All cells in the circulation are only passing from the site of formation in the marrow to the point of excretion or localization in the tissues. The mature granulocyte circulates only a short time, certainly not more than three or four days. When a cell dies in the circulation or leaves the blood stream to be excreted by a mucous membrane or to localize in the tissues, another emerges from the marrow to keep the total number at a relatively fixed level. Five to ten billion neutrophilic granulocytes are formed every day to replace those lost. Only a few cells die in the blood stream and are disposed of by the scavenger (reticulo-endothelial) cells; some die in the tissues where they have localized; the remainder are excreted through the mucous membranes of the gastro-intestinal, genito-urinary and respiratory tracts. The stimulus for the formation of new cells to replace those lost seems normally due to substances released when the nuclei of the granulocytes disintegrate. Thus, the normal picture shows a constant growth and release of new cells to replace those excreted or disposed of in the tissues or blood stream.

Under abnormal conditions of infection or toxemia, the normal marrow has an enormous capacity for supplying granulocytes. The stimulus for expansion is again a chemical one, the inciting agents being bacterial products or other toxins. The number and quality of the granular leukocytes in the circulation depend upon the need of the tissues for cells

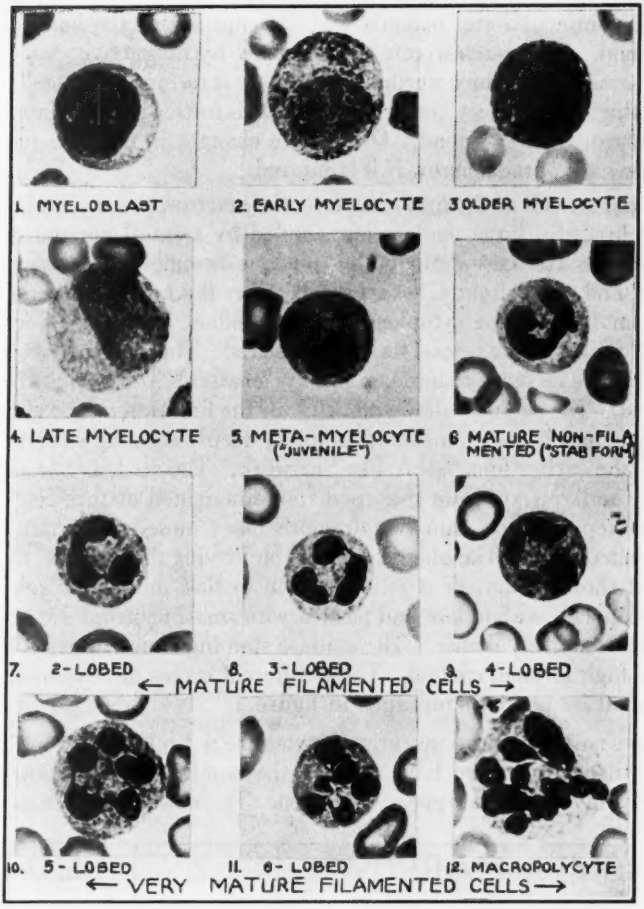

FIGURE 1: Stages in development of the neutrophilic granulocyte. (Photomicrographs x 1100.)

1. **Myeloblast:** The cell is small; the cytoplasm is scanty, basophilic and contains no granules; the nucleus is relatively large, contains nucleoli and has the characteristic "sieve" or "lace-net" pattern.

2. **Early myelocyte:** The cell is larger; the cytoplasm is more abundant, less basophilic, and contains a few granules; the nucleus is relatively smaller, still contains nucleoli and shows a "sieve" pattern.

3. **Older myelocyte:** The cytoplasm contains more granules; the nucleoli have disappeared; the nucleus is still immature but is oval and the chromatin has less of the "sieve" effect.

4. **Late myelocyte:** The cell is still larger than normal, the nucleus does not yet have the mature chromatin pattern; the granules are small and show the mature neutrophilic staining.

5. **Metamyelocyte:** The cell is now of normal size; the granules in the cytoplasm are normal; the nucleus is indented and has almost the normal chromatin pattern. This is designated a "juvenile" cell in the Schilling classification.

6. **A mature non-filamented cell:** ("stab" cell in Schilling classification).

7, 8, 9, 10. **Mature filamented cells:** In each instance, two or more lobes are united by a thin thread (Cooke's criterion).

11, 12. **Mature filamented cells:** Here there is an unusually large number of lobes indicating hypermaturity.

to combat infection and toxemia and the capacity of the bone marrow to respond. The marrow can be exhausted by overactivity or injured by the same toxins which normally stimulate it to form more cells. The circulating cells reflect the extent of the infection or toxemia if the marrow can freely respond. Qualitative changes in the cells may also show the state of the marrow if it is injured.

The parent cell of the granulocyte in the marrow, the myeloblast, consists at first of a large nucleus surrounded by a small amount of clear cytoplasm. The chromatin of the nucleus resembles a "lace-net" or "sieve" and stains lightly. As the cell grows the nucleus becomes relatively smaller and the cytoplasm more abundant. Granules develop in the cytoplasm and oxidase staining appears. The nucleoli disappear. The granules increase in number and are smaller. The nucleus becomes indented. The cell now shows motility for the first time. The chromatin of the nucleus becomes disposed in thick, deeply-staining strands rather than in the earlier fine, "sieve-like" network. The nucleus becomes still smaller and appears V- or S-shaped (non-filamented mature cell). The nucleus separates off into two or more lobes united by a thin thread (filamented cell). The older the cell is on leaving the marrow, the more lobes it shows, although it is uncommon to find more than five lobes. The cytoplasm is abundant and packed with small neutrophilic granules. The cell is actively motile. The oxidase staining is now intense, indicating the high ferment content. These different stages of development are illustrated by photomicrographs in figure 1.

Under normal conditions, granulocytes are not released from the marrow until most of them have reached the non-filamented mature stage at least and only a few appear even then. The normal release of granu-

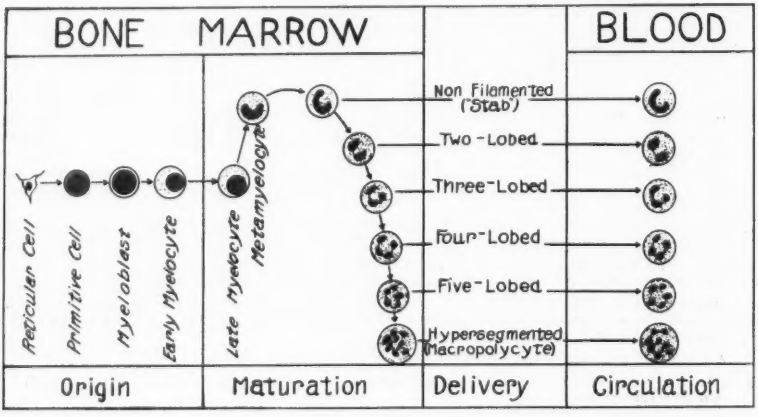

FIGURE 2: Diagram to illustrate the release of neutrophilic granulocytes after maturation.

locytes is illustrated in figure 2. Most of the new cells are filamented, having two to five lobes. If cells are being produced at a rapid rate in response to some abnormal need, the picture is different. At first, mature (filamented) cells appear. Later, a higher-than-normal percentage of less mature (non-filamented mature cells, metamyelocytes, or even myelocytes) are released. The picture in extreme cases may even simulate myelocytic leukemia where there is an unrestrained overgrowth of myeloid cells. A leukocytosis with more immature cells than normal is designated a "regenerative shift to the left."

The marrow may be injured as well as stimulated by bacteria and other toxins. It may be simply depressed so fewer cells than normal are produced in proportion to the stimulus and usually such cells are less mature than normal. This picture is designated a "degenerative shift to the left" since the immaturity of the cells results from the injury to the bone marrow which prevents normal function of the marrow. Here the cells usually show evidence of the toxic action on the marrow. The nucleus presents abnormal patterns as well as immaturity. The cytoplasm often contains basic-staining granules ("toxic" granulation) (Fig. 3). These qualitative changes in the cytoplasm may also occur with any degree of leukocytosis and even with good maturity of cells. The basic-staining granules seem to be abnormal granules and not simply an aggregation and abnormal staining of normal granules. Cells showing "toxic" granulation have a decrease in the normal granules in proportion to the number of "toxic" granules and show little oxidase staining (Fig. 4). Such cells are deficient in the ferments on which the power of defense depends, so seem of little value.

It is apparent that the age and any toxic effect on the cell can be detected by a careful quantitative and qualitative study. Myeloblasts and myelocytes are of no value as defense cells since they are non-motile. The value of a granulocyte in defense depends upon its power to invade tissues where it functions by ameboid activity as well as ferment content. The myeloblasts show no oxidase staining as well as being non-motile. Likewise, the value of cells showing "toxic" granulation, indicating damage to the cytoplasm in the bone marrow, is impaired. This is probably due to a change in ferment activity. These facts emphasize that granulocytes, to assist in defense against infection and toxemia, must be qualitatively as well as quantitatively adequate.

How should these qualitative changes be recorded? Arneth[1] (Fig. 5) was the first to emphasize the relation of age of the leukocyte to morphology. He divided the granulocytes into five classes and numerous subclasses on the basis of the number of nodes and nodulations of the nucleus. This is measuring maturity rather than immaturity. Schilling[2]

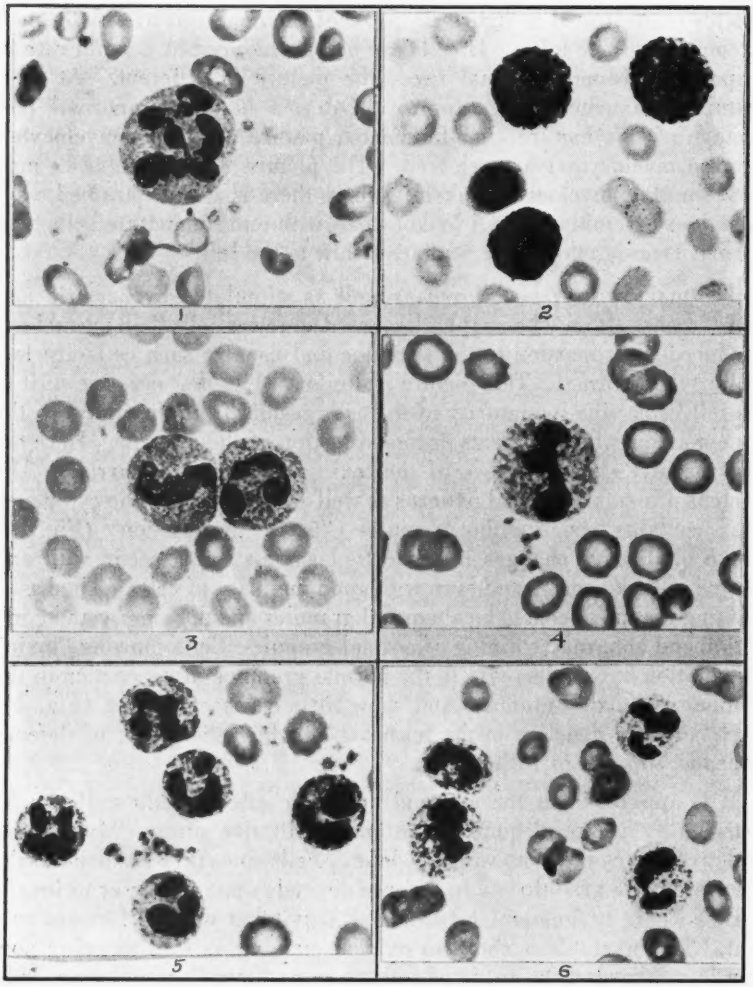

FIGURE 3: Granulation and oxidase staining of neutrophilic granulocytes illustrated with photomicrographs.

1. Normal mature neutrophilic granulocyte: Note the uniform pattern of the chromatin of the nucleus. The cytoplasm is packed with small granules of uniform size (x 1100).
2. Oxidase staining (Washburn method) of normal neutrophilic granulocytes. The cytoplasm is filled with the intense purple staining granules. The small cell is a lymphocyte which does not show oxidase staining (x 1100).
3. "Toxic" (basophilic) granulation in non-filamented (left) and filamented (right) cells. The "toxic" granules are relatively small and abundant (x 1100).
4. "Toxic" (basophilic) granulation in a non-filamented cell. The granules are relatively few in number, very large, and stain intensely. The chromatin of the nucleus is pyknotic instead of having the normal pattern as in No. 1 (x 1100).
5. Leukocytosis with marked "toxic" granulation but very good filamentation of granulocytes (x 800).
6. Oxidase stain (Washburn method) of leukocytosis of lobar pneumonia in which the cells showed marked "toxic" granulation. Note the scarcity of oxidase staining material as compared with normal in No. 2 (x 800).

QUALITATIVE CHANGES IN NEUTROPHILIC LEUKOCYTES

Basophilic Granulation Of Neutrophils With Oxidase Stain

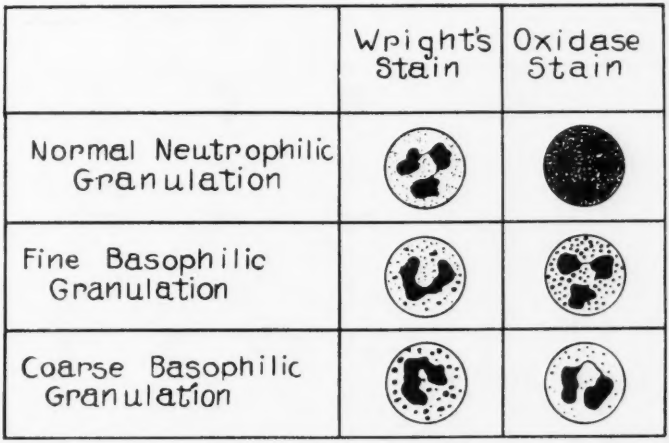

FIGURE 4: Diagram to indicate the relation between "toxic" (basophilic) granulation and the oxidase reaction.

suggested (Fig. 6) that all the segmented mature cells be placed in one group and immature cells be subdivided into myelocytes, juvenile cells (metamyelocytes), and stab cells (non-filamented mature cells). Schilling is not very definite in regard to criteria for determining a mature segmented cell. Cooke[3] suggested a cell should not be considered filamented unless two or more lobes are united by a thin thread or filament (Cooke's criterion). All classifications of maturity agree on separating mature and immature cells and the best criterion for this general division is that of Cooke. Arneth further divides the mature cells only and Schilling the immature only. The clinical value of these subdivisions is questionable. The classification suggested by Farley[4] and his coworkers is simple and is all that is needed in most cases. Here the cells are simply divided into two groups, filamented and non-filamented (Fig. 7).

If one records in the form of a graph (Fig. 8) the different stages of the granulocyte, beginning with the myeloblast on the left, the different types of leukocyte pictures seen in the circulating blood may be indicated by curves of incidence of different cell types. If more than the normal number of immature cells are present as indicated by a higher percentage of non-filamented mature cells, juvenile cells (metamyelocytes), or myelocytes, the curve of incidence appears to the left of the normal curve ("shift to the left"). This picture is found in infection and toxemia. In myeloid leukemia, the cells are still more immature so the

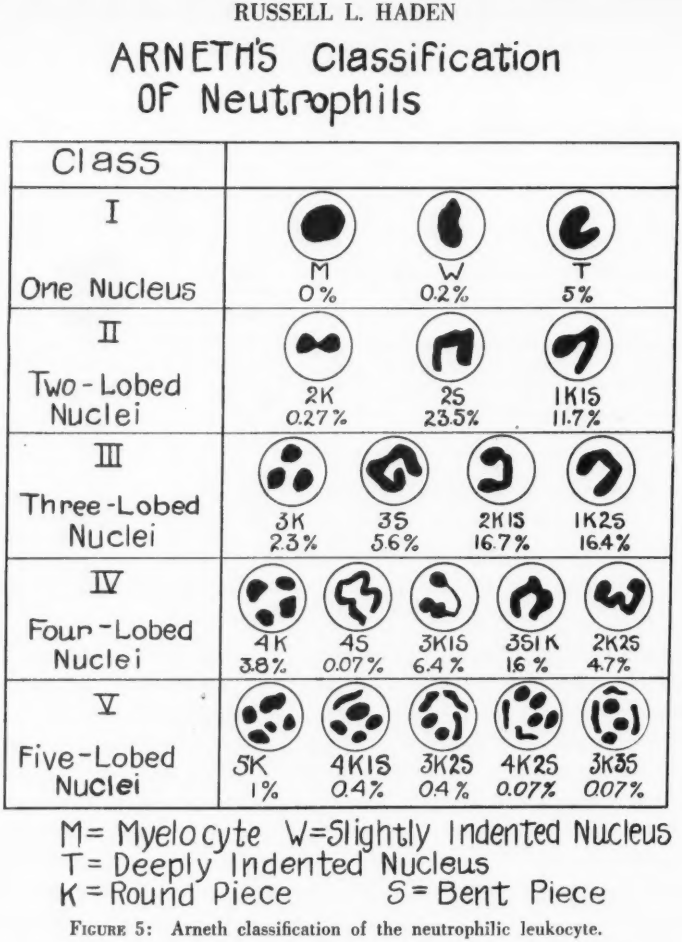

FIGURE 5: Arneth classification of the neutrophilic leukocyte.

curve is still further to the left (extreme "shift to the left"). If less than the normal number of immature cells is present and the filamented cells show many nodes, the curve appears to the right of the normal curve ("shift to the right"). This type of granulocyte reaction usually means that the granulocytes are held in the marrow longer than normal so further maturation takes place. Usually this is due to pernicious anemia where the granulocytes are mechanically enmeshed in the hyperplastic erythrogenic tissue in the red marrow. Such cells seldom show "toxic" granulation. One should not think of the leukocytes only in terms of such phases as "shift to the right" and "shift to the left" but with a fundamental understanding of what is taking place in the marrow and with an appreciation that the blood picture is dependent both upon the

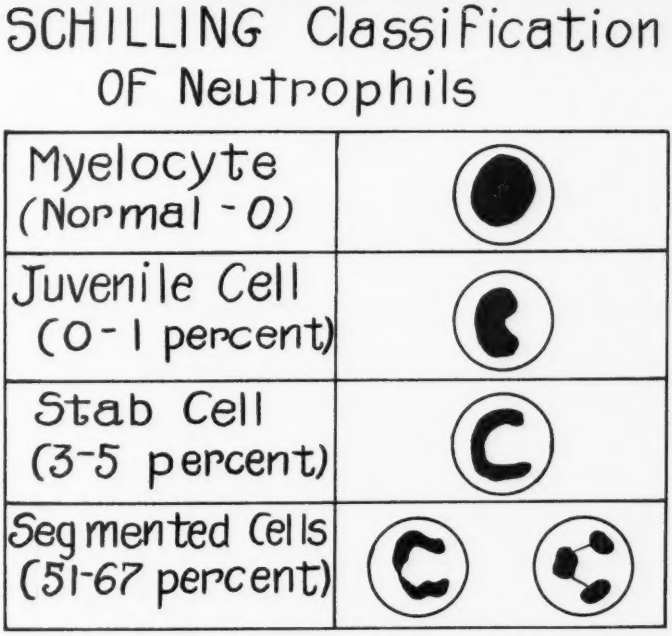

FIGURE 6: Schilling classification of the neutrophilic leukocyte.

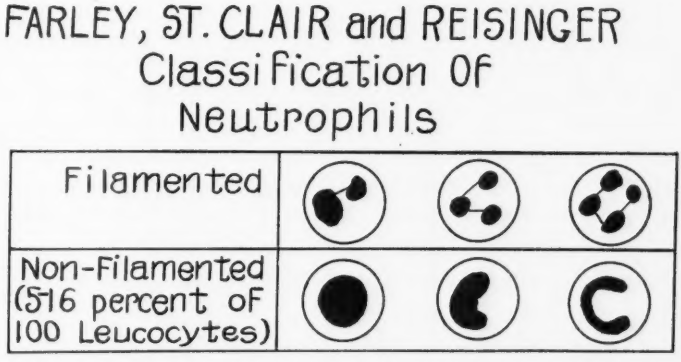

FIGURE 7: Farley, St. Clair and Reisinger classification of the neutrophilic leukocyte.

needs of the tissues and on the capacity of the marrow to respond to stimulation.

The presence of "toxic" granulation is equally as important as maturity of the granulocytes in gauging the activity of a toxic process. There is no very satisfactory quantitative method for recording "toxic" granula-

TABLE 1

	Total per cent	*Normal per cent*	*"Toxic" Granulation per cent*
Polymorphonuclear neutrophils, filamented	60	12	48
Polymorphonuclear neutrophils, non-filamented	25	5	20
Polymorphonuclear eosinophils	0		
Polymorphonuclear basophils	0		
Lymphocytes	10		
Monocytes	5		

$$\text{Degenerative index} = \frac{\text{Number of neutrophils showing "toxic" granulation}}{\text{Total number of neutrophils}} = \frac{68}{85} = 80$$

Percentage of neutrophils showing "toxic" granulation ..... = 80

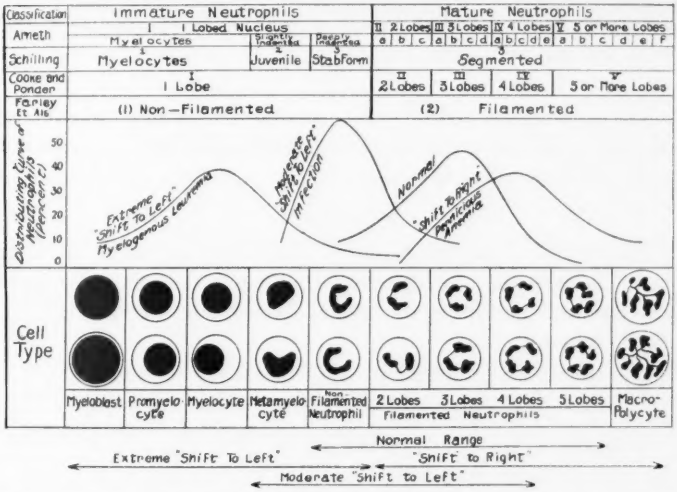

FIGURE 8: Diagram to correlate the different classifications of the neutrophil.

tion except to indicate the percentage of cells showing such changes and to use descriptive terms as mild, moderate, severe, and extreme to record the extent of the granulation. Kugel and Rosenthal[5] suggest a degenerative index based on the percentage of neutrophilic granulocytes showing basophilic or "toxic" granules. A differential count which measures satisfactorily the extent of immaturity of the neutrophilic granulocytes as well as the frequency of basophilic or "toxic" granulation is shown in Table 1.

The interpretation of qualitative changes in the neutrophilic granulocyte may be summarized as follows:

1. A neutrophilic leukocytosis with mature normal cells indicates the presence of an infection or toxemia to which the marrow is fully able to respond.

2. A neutrophilic leukocytosis with less mature cells or a significant increase in immature cells without an increase in the total count indicates either:

a. Some difficulty in response of the marrow to an infection or toxemia.

b. An overwhelming infection or toxemia requiring the marrow to deliver many granulocytes.

3. A normal count with some increase in immature cells indicates a mild infection or toxemia.

4. A leukopenia with immature cells indicates a depression of the marrow preventing the normal reaction to infection or toxemia.

5. A leukopenia, normal count, or leukocytosis with more mature cells than normal indicates that the cells are retained in the marrow without injury to the cells so that excessive maturation takes place.

6. The presence of "toxic" granulation with or without a leukocytosis and regardless of the maturity of the cells, indicates an infection or toxemia which is injuring the marrow.

Summary

1. The correct interpretation of qualitative changes in granular leukocytes in reference to maturity or "toxic" granulation requires a fundamental understanding of factors influencing the development of cells in the marrow.

2. The filament non-filament count measures satisfactorily in most cases the degree of maturity of the neutrophilic granulocytes.

3. Basophilic or "toxic" granulation indicates the presence and severity of a toxemia affecting the marrow.

4. The value of the cells in defense depends on the quality of the cells even more than the number.

5. The interpretation of qualitative changes has been summarized.

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CELIAC GANGLIONECTOMY IN RAYNAUD'S DISEASE

Further Report

GEORGE CRILE, M. D.

A year ago (July, 1937) I reported in this journal[1] the immediate results of bilateral celiac ganglionectomy in a case of Raynaud's disease.

Complete relief from the symptoms was experienced almost simultaneously with the completion of the first ganglionectomy (left) and at the time the above cited article was written this relief from pain had persisted for six weeks.

In this case the symptoms of Raynaud's disease had been present for 15 years and for five years had been so pronounced that the patient had been unable to work. The pain in his fingers was so severe that he had to resort to morphine to relieve the pain. The fingers would become red, white, and then blue, and were ice cold even in hot weather, and there was a loss of sensation in both the hands and the feet. Because of gangrene two fingers, one on each hand, had been amputated two months before we saw the patient.

In June, 1938, one year and one month after the celiac ganglionectomies had been performed, the patient reported that he had been symptom-free since the operation. He had had no pain in the fingers or toes even during cold weather. Even two months after the operation the hands showed no blanching after immersion for ten minutes in ice water. Physical examination revealed good radial pulsations, good skin texture, and a warm and dry skin.

Doctor Zeiter, who measured the skin temperature, reports that the two readings taken at this time were consistent and were two degrees higher than the average when the patient was first seen.

In the previous article we reported the abnormal size of the celiac ganglia in this case—left 1010 mg., right 535 mg. This large size of the ganglia which is comparable to the size in many cases of hypertension, when considered together with the results of their removal, suggest that Raynaud's disease as well as hypertension is due to a pathologic physiology of the celiac ganglia, the size of which appears to be an inherited characteristic.

The results in this case which have now persisted for more than a year, and the fact that ganglionic tissue cannot be regenerated indicate that the celiac ganglion is the logical point of attack in the treatment of Raynaud's disease.

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BIOPHYSICAL FOUNDATIONS OF SUPERVOLTAGE ROENTGEN THERAPY

OTTO GLASSER, PH.D.

During the past eight years, the routine 200 kilovolt deep therapy roentgen machines have been supplemented by supervoltage roentgen therapy apparatus. Some of these are operated at voltages in excess of one million volts. There are about twenty-five roentgen therapy transformers for voltages of 400 KV in the United States and ten machines operating at approximately one million volts. Most of the latter are rather bulky and expensive, some even requiring special buildings.

Different methods of generating supervoltages are employed as, for example, an induction coil (Memorial Hospital, New York City), cascaded transformers with valve tube rectification for the production of constant or pulsating high potentials (Mercy Hospital, Chicago, 800 KV)

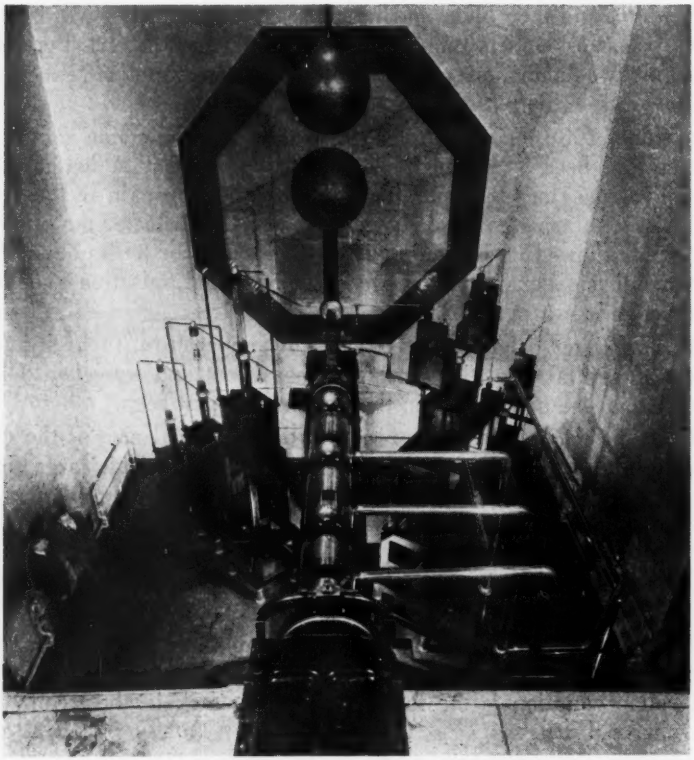

FIGURE 1: General Electric 800 KV roentgen ray constant potential transformer generator with cascaded glass tube. Target of tube lies under heavy lead cover in front center of picture. Roentgen rays are projected downward into the treatment chamber.

(Fig. 1), (Charles T. Miller Hospital, St. Paul, 1200 KV) (Fig. 2), the more recent Sloan resonance oscillator (Crocker Cancer Institute, New York City, 1000 KV) (Fig. 3), and the Van de Graaff static generator (Huntington Memorial Hospital, Boston, 1250 KV) (Fig. 4).

Different types of x-ray tubes also are being tried with these high voltage equipments—cascaded glass tubes (Fig. 1), Crane-Lauritsen porcelain tubes (Fig. 2), cylindrical porcelain tubes (Fig. 4), or the Sloan tube which is an integral part of the Sloan oscillator (Fig. 3). Only those x-ray tubes for voltages up to 400 KV are sealed off after the

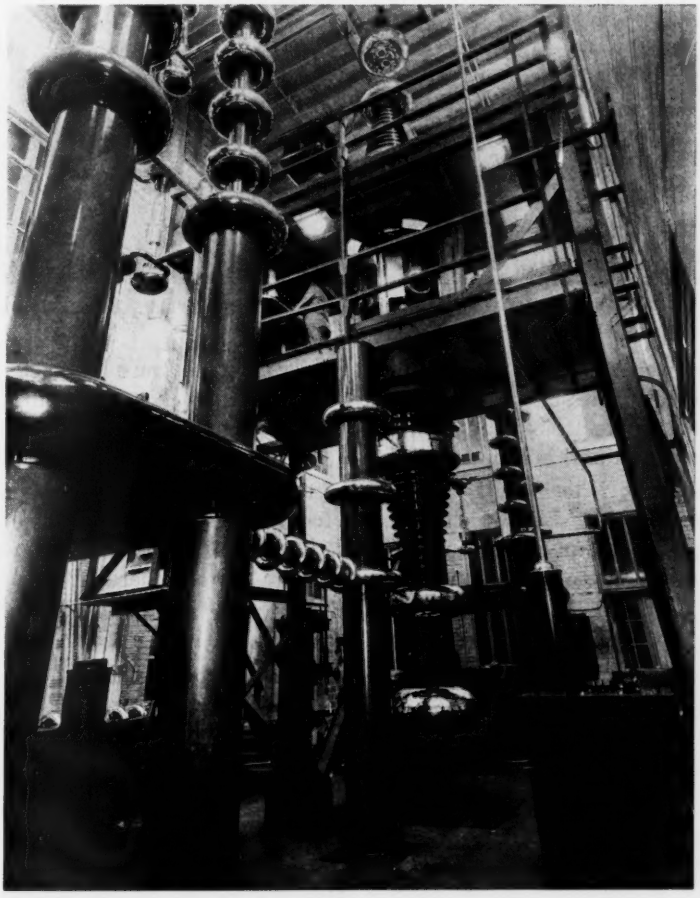

FIGURE 2: Kelley Koett 1200 KV roentgen ray constant potential transformer generator with double Crane-Lauritsen porcelain tube. For comparative size, note operator at switchboard on platform.

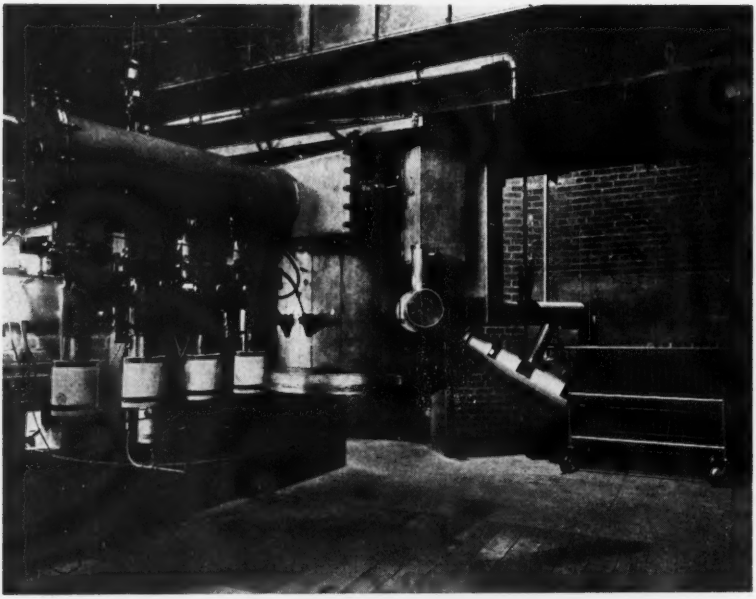

FIGURE 3: Sloan 1000 KV roentgen ray resonance oscillator generator. Battery of vacuum pumps at the left, treatment cones at the right.

gas is evacuated from them. Tubes of higher voltages must be evacuated continuously which necessitates the constant attendance of technically trained personnel as may be appreciated by figure 3 which shows the battery of pumps in connection with the Sloan apparatus.

One who is technically inclined must marvel at these new products of engineering skill which have overcome the greatest experimental difficulties within a few years. The radiotherapist will ask, "What are the advantages of supervoltage therapy over 200 KV therapy?"

From a purely biophysical point of view, the advantages of supervoltage therapy may be enumerated as follows:

1. The output of radiation is greater, thus permitting the use of heavy filters and larger focal skin distances which produce larger depth doses.

2. Greater penetration which results in higher half-value layers or also in larger deep doses.

3. The extremely short and penetrating rays may possibly have selective effects in tissues or other matter.

4. It is possible to produce new types of rays such as neutrons, high-speed cathode rays, and, finally, artificial radio-active substances with unknown biological effects.

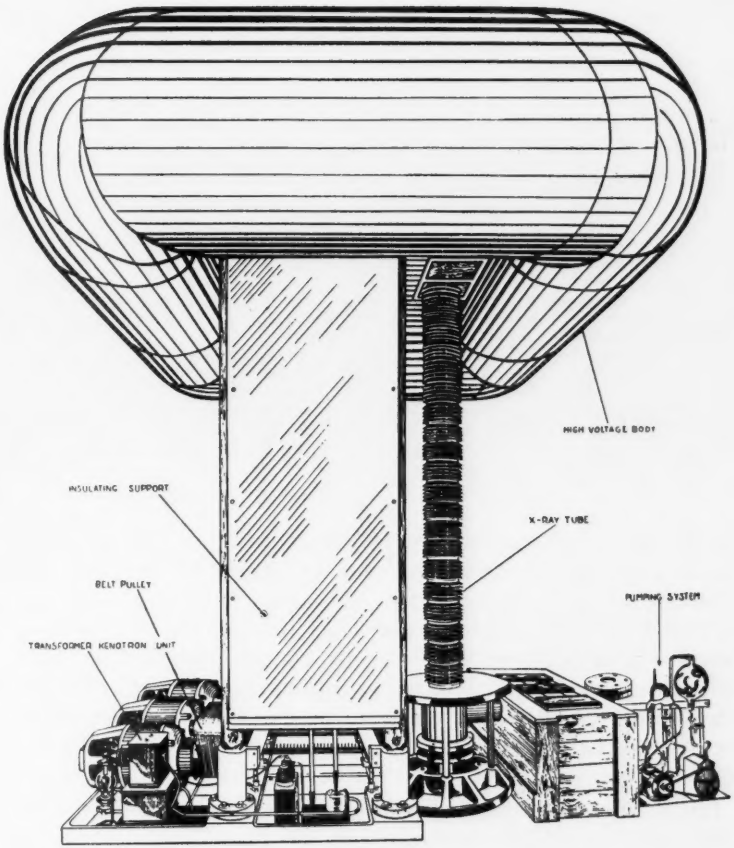

FIGURE 4: Van de Graaff 1200 KV roentgen ray generator. Rotating belts within the insulating support are charged by a transformer Kenotron unit (bottom) and deposit this charge on the high voltage body (top). Here these collected charges raise the potential to over one million volts. X-ray tube at the right side from the high voltage terminal projects through the floor into the treatment room below. See figure 5.

Table 1 presents a comparative list of radiation intensities in r per minute and of radiation qualities in half-value layers, as well as deep doses with different voltages and filters.

The last column of Table 1 is of especial interest. It shows that the percentage of radiation penetrating to a depth of 10 cm. below the skin surface increases from 33 per cent to 50 per cent if the voltage is raised from 200 kilovolts to a million volts. A graphic picture of this increase for a uniform distance of 80 cm. is shown in figure 6. Although deep doses of 50 per cent can also be approximated with roentgen rays pro-

TABLE 1

KV Peak	*MA*	*Type of Apparatus*	*Focal Distance in cm.*	*Filter in mm.*	*r/min. in free air*	*Half-value layer in mm.copper*	*Deep dose at 10 cm. 10x10 cm. area*
200	5	Transformer, constant potential, valve tube rectification	50	1 Cu + 1 Al	13.0	1.5	33
400	5	Transformer, constant potential, valve tube rectification	60	5 Cu + 1 Al	30.0	7.0	40
800	10	Transformer, constant potential, valve tube rectification (Mercy Hospital, Chicago)	70	1 Pb + 3 Cu + 3 brass + 1.56 Sn	36.0	8.2	48
1200	1	Van de Graaff static constant potential (Huntington Memorial Hospital)	70	6 Pb (equivalent)	60.0	10.5	51

duced at lower voltages by using very heavy filtration and by increasing the focal skin distance, the quality of the million volt beam is entirely different and more homogeneous (10.5 mm. half-value in copper as compared with 1.5 mm. half-value layer in copper for 200 kilovolts). Practically, this difference finds its expression in the fact that the dose which the skin can tolerate increases with the hardness of radiation. In other words, a relatively greater amount of radiation can be applied to deeper seated tissue with the 1000 KV rays than with 200 KV rays before the tolerance of the skin is reached.

It is also possible that short-wave radiations may have definite selective effects for certain tissue cells, although there is still considerable doubt about it because conclusive evidence can be accumulated but slowly.

The last advantage of using supervoltage roentgen therapy apparatus, namely, the production of new types of rays, has spurred investigators in various parts of the world to encourage construction of high voltage equipment to even higher potentials. With voltages of about three million volts, it is possible to produce x-rays of a higher penetration than the most penetrating gamma rays of radium and with many times the intensity of the total amount of all the concentrated and purified radium in the world. With such potentials, cathode rays consisting of electrons of extremely high speeds can be produced. Such cathode rays have intensely destructive effects on tissues and they show very favorable distribution characteristics within the tissues under certain conditions.

Furthermore, these high potentials permit the production of neutron rays of extremely high velocity. Preliminary experiments have shown

FIGURE 5: Lower end of 1200 KV roentgen ray tube (see fig. 4) in treatment room.

that neutron rays may be superior to x-rays in their biological activity. Neutron bombardment of certain substances leads to nuclear disintegrations and the production of artificial radio-active substances. Such substances can be activated for definite periods of time and may have definite therapeutic uses. Substances can be activated which are selectively absorbed in organs to be treated—for example, radio-iodine may be used for the treatment of diseases of the thyroid gland and

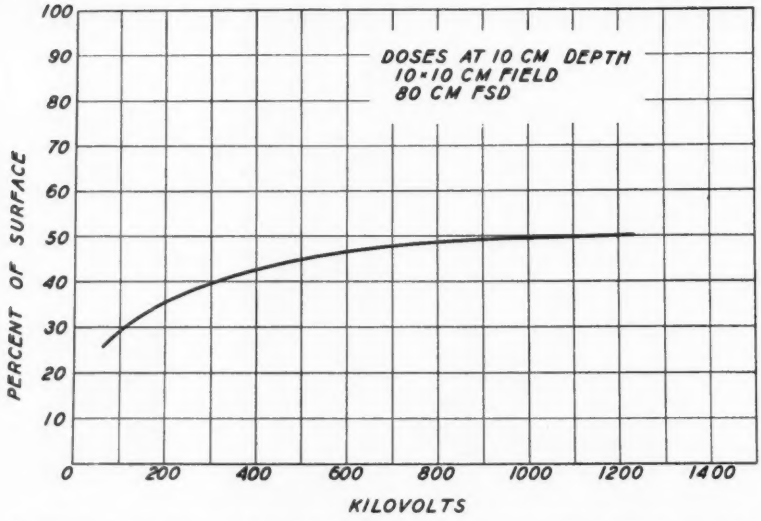

FIGURE 6: Deep doses at 10 cm. depth in per cent of surface doses (80 cm. focal skin distance, 10 x 10 cm. port of entry) for various roentgen ray voltages. Measured with a Glasser-Seitz condenser dosimeter with air wall chamber on a purple heart wood phantom.

radio-calcium or radio-phosphorus for the treatment of bone diseases, etc. There can be no doubt that these different types of rays open an entirely new field of therapy.

Although roentgen therapy by supervoltages may not offer startling advantages over treatment by 200 kilovolts, still from a biophysical point of view, increasing the voltage offers the possibility of an entirely new series of weapons in the fight against certain diseases.

DIAPHRAGMATIC HERNIA

JOSEPH C. ROOT, M.D. AND CLARK P. PRITCHETT, M.D.

In differential diagnosis in the presence of atypical symptoms referable to the upper abdomen or cardiorespiratory system, diaphragmatic hernia must be given serious consideration by clinicians and roentgenologists. This condition, which is not now an uncommon finding during the roentgen examination of the gastro-intestinal tract, may or may not give rise to clinical signs and symptoms. It is interesting to note that previous to 1923, Pancoast and Boles[1] were able to find only 47 cases in the literature, whereas, in recent years many reports containing long series of cases have appeared. In our own series, there are 31 cases which were found during the routine examination of 2,213 stomachs, an incidence of 1.4 per cent.

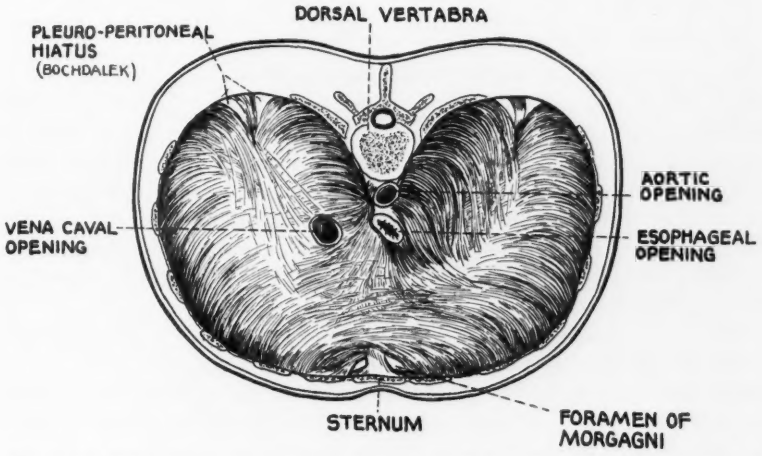

FIGURE 1: Schematic drawing showing foramina of Bochdalek formed by the failure of fusion of the pars lumbalis and pars costalis, and foramina of Morgagni formed by failure of fusion of the pars costalis and pars sternalis. These openings give rise to congenital diaphragmatic hernia.

CLASSIFICATION

For the purpose of clarifying the classification of diaphragmatic hernia, it will be well to include associated conditions commonly accepted as herniae. Although many classifications have been presented and are of interest, insofar as determining whether the hernia is true or false, congenital or acquired, etc., many give little aid in determining the type of treatment that is to be given the patient. Probably one of the most practical classifications is the following one presented by

Marks,[2] and which we feel gives the clinician the maximum amount of information from the roentgen examination.

1. Thoracic stomach.
   Esophagus very short
   Entire stomach in the thorax above the diaphragm
2. Diaphragmatic hernia with short esophagus.
   Part of the stomach above the diaphragm with a congenitally short esophagus
3. Hiatus hernia—esophagus of normal length.
   Esophagus not forming part of the hernia (para-esophageal)
   Esophagus forming part of the hernia
4. Congenital hernia.
   Other parts of the gastro-intestinal tract—the colon or small intestine—are usually involved. Most common through foramen of Bochdalek and Morgagni (Fig. 1).
5. Traumatic hernia.
6. Congenital absence of the diaghragm.

Two conditions are listed above, namely, thoracic stomach and diaphragmatic hernia with short esophagus, which in the true sense are not herniae since the displaced organs have never been in the abdominal cavity, but have always been either entirely or partly in the thorax. They are, however, commonly considered as herniae and hence are classified as such for practical purposes. Another condition, eventration of the diaphragm, is occasionally classified with diaphragmatic hernia and certainly must be considered in the differential diagnosis of lesions of the diaphragm.

Thoracic stomach is a rare condition and one that is a developmental anomaly. When this occurs, the esophagus is usually very short and the stomach may be entirely within the thorax. In some of the cases which have been reported, however, a portion of the distal end of the stomach has been below the level of the diaphragm. The stomach may be surrounded by a serous sac which communicates with the peritoneal cavity, and, as a rule, is the only organ involved in the abnormal position. Thoracic stomach may give rise to very few symptoms, and longevity of life is not incompatible with such a condition since in some of the reported cases the patients have lived beyond the age of seventy.

Diaphragmatic hernia with short esophagus is another developmental anomaly but one which may not be as obvious to the examiner as those in the preceding group. In this type, the esophagus is likewise short but generally terminates a short distance above the diaphragm; hence a part of the pars cardiaca of the stomach is above the level of the diaphragm. It is very important to differentiate herniae in this group from the hiatus hernia since surgery, here, if contemplated, would do little good, due

to the shortness of the esophagus and the impossibility of placing all of the stomach within the abdominal cavity.

Since it is not reducible, this hernia may be apparent during the roentgen examination while the patient is in the upright position. In contour, the upper portion of the stomach is usually pointed and the esophagus empties into this upper or peaked portion. The supine position should, of course, be employed in the examination of every suspected

FIGURE 2: Diaphragmatic hernia with short esophagus. The esophagus empties into the most superior portion of the pars cardiaca; a pointed contour is produced.

FIGURE 3: Hiatus hernia. Contour of stomach is round in upper portion.

diaphragmatic lesion and careful observation made with the fluoroscope during the swallowing of the opaque meal. A typical example of diaphragmatic hernia with short esophagus is shown in figure 2. In this illustration, the characteristic peaked contour of the intrathoracic pars cardiaca is quite apparent.

Diaphragmatic hernia of the hiatus type is perhaps encountered more commonly than any other. In this series, 29 cases or approximately 93

per cent of the total number were of this type. This is a higher percentage than is generally reported but it may be accounted for partly by the fact that the majority of our gastro-intestinal examinations have been made in ambulatory adults. The esophageal hiatus is a muscular one and it is conceivable that there occurs some relaxation of the ring as the age periods are more advanced. In table I is given the age incidence as well as the sex of those in whom we have found herniae. It will be noted that the greater number of patients have been in the decades from 50 to 70 years.

TABLE I

Age and Sex Incidence of Diaphragmatic Hernia

Age in years	*30—40*	*40—50*	*50—60*	*60—70*	*70—80*	*80—90*	*Total*
Male	1	2	3	5	3		14
Female	1	2	5	6	2	1	17

Although this group has not been subdivided in many classifications, we have tried to establish two subgroups. This, of course, is of no value from a therapeutic viewpoint but is chiefly of interest from the point of diagnosis. We have designated the para-esophageal class as those in which the esophagus remains fixed below the diaphragm and does not form a part of the hernia. The other class under this general group comprises those in which the esophagus forms a part of the hernia. Typical examples of these are seen in figures 3 and 4. In the illustration of para-esophageal hernia (Fig. 4), the esophagus may be seen in its normal position not forming a part of the hernia. The number of this type that we found in this series was six, or approximately 20 per cent of the total number of herniae.

One of the characteristic features of the *hiatus* group from the roentgen viewpoint is the rounded contour of the herniated part of the pars cardiaca. This, it will be noted, is quite different from the contour seen in the preceding group in which the superior portion of the pars cardiaca is generally pointed. Another feature is the finding that the distal end of the esophagus enters the stomach in its normal position. Since this type of hernia is amenable to surgical treatment, it is important to determine whether or not the esophagus is of normal length, thereby classifying the hernia as one of the hiatus group.

The *congenital herniae* are usually found in infants and children and are due to failure of fusion of the segments of the diaphragm. They occur most commonly on the left side and through the foramen of Bochdalek. The less common form of congenital hernia will be through the foramen of Morgagni, either on the right or left side. In the congenital hernia, organs other than the stomach are generally involved—both the small

FIGURE 4: Hiatus hernia of para-esophageal type. Esophagus does not form a part of hernia and can be seen in its normal position.

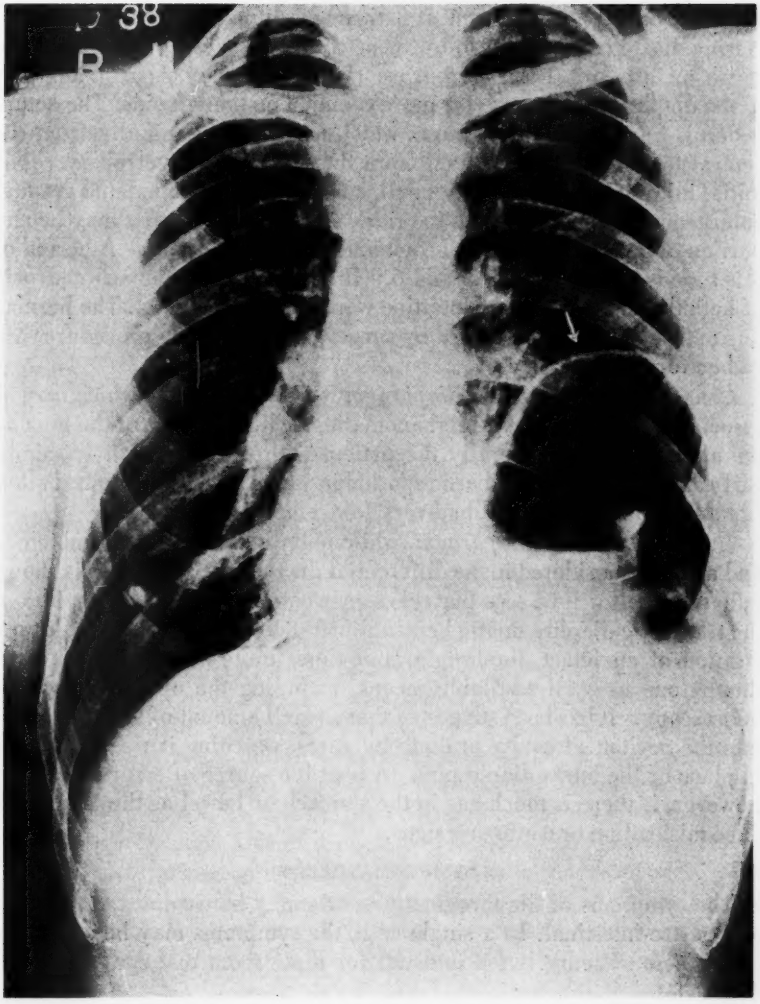

FIGURE 5: Traumatic diaphragmatic hernia as it appears in chest film. Fluid level can be seen in the stomach.

and large intestine, omentum, spleen, and the left lobe of the liver. Early death is the rule in these cases, due either to asphyxia or intestinal obstruction. The diagnosis is, of course, obvious following a few swallows of barium solution. No case of this type occurred in our series.

Trauma is thought by some observers to be responsible for one-third of all diaphragmatic herniae. In this series, there is only one case but

this is probably due to the type of patients examined, as noted previously. Hernia due to trauma may follow penetrating injuries, the most common cause, or falls and crushing injuries. While they may occur in any part of the diaphragm, they are far more common on the left side. The actual lesion is a tear in the diaphragm which usually runs radially from the central tendon and may extend from the dome to the periphery. The initial injury may be relatively small, as from a bullet wound, but gradual enlargement of the opening is the rule. The herniated parts may be any portion of the gastro-intestinal tract and associated organs. A hernia of this type is seen in figures 5 and 6. In this case, the stomach and part of both the small and large intestine were within the thorax. The herniae due to trauma may be repaired by surgery although such procedures are rather formidable.

Congenital absence of the diaphragm is a rare condition which may be associated with other congenital anomalies such as absence of the lung on the affected side. Generally the patient with this condition succumbs early although cases have been reported in which they have reached adult life and, strangely enough, had very few symptoms.

Eventration of the diaphragm, while not a hernia, may resemble one and must be considered in the differential diagnosis. Such a case is shown in figure 7. It will be seen that this somewhat resembles the chest film of the traumatic diaphragmatic hernia illustrated in figure 5. The demonstration of an intact diaphragm is at times quite a difficult task even though one uses all available means, including the opaque meal and fluoroscopy. It has been suggested that a small amount of air be injected into the peritoneal cavity in doubtful cases, watching it rise to be held in place by the intact diaphragm. A possible source of error may arise, however, if there is much gas in the stomach or bowel as they may produce misleading or confusing signs.

Symptomatology

The symptoms of diaphragmatic hernia may be cardiac, respiratory, and gastro-intestinal. In a single case, the symptoms may be attributed to all these systems, but it is usual for those from one system to predominate.

In cases in which there is dysphagia, the clinician's attention is directed early toward the esophagus, and he is apt to think of cardiospasm or carcinoma of the esophagus, requesting roentgen examinations with these lesions in mind. Dysphagia occurs chiefly in the herniae with a short esophagus but it also may be present with other types. The dysphagia is usually the intermittent, not the progressive, type seen with carcinoma of the esophagus, and frequently it occurs only at the end of a heavy meal. Patients observe that they do not have symptoms if they eat a "light diet." Relief from dysphagia follows vomiting. Four of our

TABLE II

Patients with Diaphragmatic Hernia Having Symptoms

	No.	*Average Age*	*Sthenic*	*Normal Habitus*	*Asthenic*	*Average Duration of Symptoms*	*Cardio-respiratory Symptoms*	*Gastro-Intestinal Symptoms*		
								Dysphagia present	*Simulating ulcer*	*Simulating gallbladder disease*
Males	7	58.4	4	3	0	3.3yrs.	4	2	3	0
Females	5	59.4	4	1	0	11 yrs.	0	2	2	3

twelve patients who had symptoms complained of dysphagia as shown in table II.

Patients with diaphragmatic hernia frequently have symptoms that simulate peptic ulcer or the hyperacidity syndrome. As shown in the table, five of our patients experienced such symptoms. The most prominent clinical features are epigastric distress, pain, or cramps occurring one-half to one hour after meals and made worse by food and relieved by vomiting. Relief may also be obtained by a bowel movement, passing flatus, belching, or taking an enema, these measures tending to change the intra-abdominal pressure. The symptoms may occur intermittently, they may be present after only one meal such as the evening meal which is usually the heaviest, or they may be present only when the patient eats before retiring. One of our patients, a fifty-six year old woman who had symptoms very suggestive of peptic ulcer, had had two episodes of hematemesis. Careful roentgen examination revealed a moderate sized hiatus hernia but no evidence of peptic ulcer. It is probable that the hermorrhages were due to erosions of the gastric mucosa at the site of the constricting ring of the hernia.

Diaphragmatic hernia at times causes symptoms which lead the clinician to think of chronic disease of the gallbladder. The patients complain of pain in the upper right quadrant radiating at times to the epigastrium or to the back. The attacks of pain come on during the course of a heavy meal or after the meal is eaten. Nausea and vomiting may follow later, usually relieving the discomfort. The distinguishing feature is the fact that with diaphragmatic hernia simulating cholecystitis there is usually no residual tenderness in the upper right quadrant after the pain passes. Drainage of the gallbladder will reveal normal findings, cholecystography shows normal findings, and the roentgen studies of the

FIGURE 6: Stomach in thoracic position with pylorus pointing downward.

gastro-intestinal tract reveal the hiatus hernia. Table II shows that three of our patients, all women, had symptoms that led the clinician to make a diagnosis of gallbladder disease.

Symptoms of cardiorespiratory disease must be distinguished carefully from those produced by diaphragmatic hiatus hernia. The patients may complain of symptoms which very closely simulate angina pectoris; there may be pain beginning in the precordium or in the epigas-

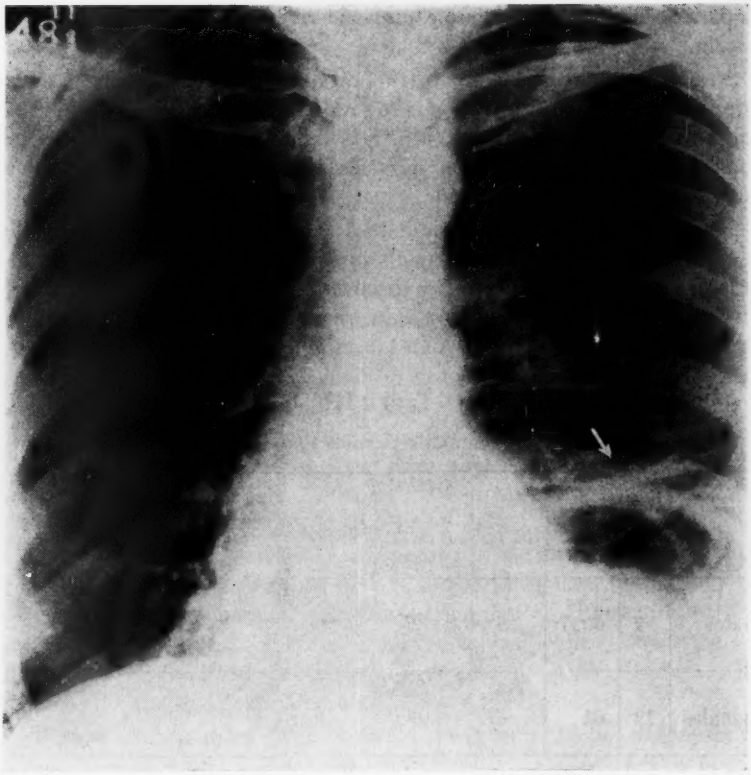

FIGURE 7: Eventration of diaphragm showing resemblance to traumatic hernia in figure 4.

trium and radiating to the left shoulder or down the left arm occasionally. To distinguish these cases from those of true angina pectoris, the relationship of the pain to exertion, the electro-cardiographic tracings, and roentgenograms of the stomach and esophagus must be carefully evaluated. One of our patients who had symptoms simulating angina pectoris due to a small diaphragmatic hernia also had true angina pectoris.

Some patients complain of pain in the region of the ensiform cartilage, severe dyspnea, and cyanosis while eating or shortly after eating. One such patient had attacks very frequently and always obtained relief when he could feel the food pass from the thoracic portion of his stomach to the abdominal portion. Another patient who, while eating, had severe dyspnea and pain in the region of the ensiform cartilage, obtained relief by vomiting, belching, or passing flatus. As shown in table II four of our

12 patients with symptoms had complaints referable to the cardiovascular system.

Strangulation or complete obstruction of the hernia may occur. The symptoms of these complications are sudden severe pain in the left upper epigastrium which is only slightly relieved by morphine. Severe and persistent vomiting soon ensue. Physical examination reveals rigidity of the upper part of the abdomen.

Many cases of diaphragmatic hernia are asymptomatic. Nineteen of our thirty-one patients had no symptoms which might be ascribed to the hernia. The herniae were either discovered during the course of a complete clinical laboratory survey or were found to be incidental to some other gastro-intestinal disease. In table III is shown the frequency with

TABLE III

Patients with Diaphragmatic Herniae that Were Asymptomatic

	No.	*Average Age*	*Sthenic*	*Normal Habitus*	*Asthenic*	*Associated diverticulosis*	*Associated gallbladder disease*	*Cancer elsewhere in body*
Males	7	60.7	5	2	0	2	4	1
Females	12	61	6	6	0	5	2	1

which other pathologic states occurred in these patients with asymptomatic diaphragmatic hernia. The demonstration of a diaphragmatic hernia must not deter the roentgenologist and the clinician from a thorough investigation of the remainder of the gastro-intestinal tract. Seven of the patients who had asymptomatic diaphragmatic hernia had diverticulosis of the colon as an associated roentgen finding and in one case there was a large diverticulum of the third portion of the duodenum. Six cases showed either nonvisualization of the gallbladder with the cholecystographic dye or cholelithiasis, or both.

PHYSICAL SIGNS

Only with the large hiatus herniae will physical signs of diaphragmatic hernia be evident. The examiner may encounter asymmetry of the chest with the ribs more widely separated on the affected side and a flare of the costal margin that is noticeable on the affected side. Percussion may reveal a tympanitic note which may be limited to the base of the lung or may be elicited higher toward the axilla. Shifting the position of the

patient may cause a marked change in the physical findings—from tympanitic to dull—if fluid replaces air in the area being examined. Percussion may also reveal failure of the left diaphragm to descend. On auscultation of the chest, a high-pitched tinkling sound may be heard, or gurgling and splashing sounds may be audible.

Diagnosis

The diagnosis of diaphragmatic hernia is almost entirely dependent upon the roentgen examination. The existence of the condition may be suspected from a film of the chest, but for accurate diagnosis it is necessary to employ the opaque meal and both the fluoroscopic and radiographic techniques. During this examination, it is essential that the patient be observed in the supine position with head lowered as well as the upright and prone positions, since it is by means of the first named position that the majority of herniae will be discovered. Particular attention should be devoted to determining the length and position of the esophagus as noted in the foregoing paragraphs on the classification of the various types of herniae.

The mere presence of a hernia may be determined at the time of a laparotomy by palpating the esophageal opening in the diaphragm. The type of hernia cannot be determined by this method although the amount of relaxation can be accurately noted by the number of fingers that can be passed through the relaxed ring. This procedure has its greatest value, of course, after the presence and type of hernia has been determined by means of the roentgen examination.

Physical examination alone is not of great value in the diagnosis of this condition. While large herniae may be found to be present by physical findings, the majority of cases would be missed, since by far the greater number of herniae are small or of only moderate size. The history is often suggestive of such a condition, but it usually simulates other pathological conditions such as ulcer or gallbladder disease. Hence, to make a diagnosis from the history alone would be quite hazardous.

Treatment

In the medical management of patients with diaphragmatic hernia, the patient should be instructed to eat small meals frequently and to maintain an erect posture for a period of several hours after meals. It is inadvisable for the patients to eat before retiring at night and even with these precautions, some patients will find it more comfortable to sleep in a semirecumbent position.

If the gastro-intestinal symptoms are not sufficiently relieved following medical management, if there are frequent and severe attacks of cardiorespiratory symptoms, or if there is danger of obstruction or strangulation, surgery must be resorted to. Reduction of the hernia

and repair of the diaphragm may be made either by a thoracic or abdominal approach. In some cases, it is advisable to do a preliminary phrenicotomy. Obviously, cases with a short esophagus cannot be helped by surgery.

Summary

Diaphragmatic hernia is a condition which is being recognized with increasing frequency. In this group, 31 herniae were discovered during the course of 2,213 consecutive roentgen examinations of the stomach—an incidence of 1.4 per cent.

The majority of herniae so found are incidental and asymptomatic, only 12 of this group having symptoms that could be ascribed to the hernia.

Diaphragmatic hernia presents no characteristic symptoms. The most important in this group were dysphagia and symptoms simulating cardiorespiratory disease, hyperacidity syndrome, and gallbladder disease.

In the diagnosis of diaphragmatic hernia, the roentgen examination is the most important procedure, with emphasis placed upon the supine position with the head of the patient lowered.

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RHINOPHYMA

Report of a Case

R. S. Dinsmore, M. D., and K. W. Keller, M. D.

Occasionally, a marked hypertrophy of the nasal tissues and enlargement of the sebaceous glands develop in patients with acne rosacea, resulting in a large, bulbous nose. To this condition, the name rhinophyma is applied. The nasal enlargement may appear simultaneously with the onset of acne rosacea but more frequently it develops several years later. Involvement of areas other than the nose is rarely seen, although Sams[1] reports a case with marked tumefaction of the chin, and mentions several cases where tissues adjacent to the nose were involved. Rhinophyma rarely occurs in women. All six cases treated at the Cleveland Clinic since 1930 have occurred in men.

A specific etiological factor for the parent disease, acne rosacea, has not been definitely discovered. Among the contributing causes have been mentioned excessive use of alcohol, liver disease, constipation, folliculitis of the face, exposure, substitution of cleansing creams for soap and water, and focal infection[2].

Ayres and Anderson[3] reported 77 cases of acne rosacea and pityriasis folliculorum in which large numbers of Demodex folliculorum were found in the pustules. There was a marked reduction in the number of parasites and remarkable improvement or cure following the application of an antiparasitic ointment. They believe they have discovered a significant etiological factor for acne rosacea.

The following case illustrates a typical rhinophyma and a type of treatment which, in our experience, has given a very satisfactory result.

Report of Case

The patient was a white, single man, 41 years of age, who came under observation in December, 1937, with the complaints of an acne-like eruption on the face and marked enlargement of the nose. Fifteen years prior to admission there appeared on his face a moderate erythema with superimposed papules and pustules. The nose, which was also involved in this eruption, began to enlarge slowly until, at the time of our examination, it was four or five times the normal size, most of the enlargement having occurred during the preceding three years. The eruption had persisted unabated throughout this period, and there were many pitted scars on the cheeks, forehead, nose, and chin. There was no pain, tenderness, or pruritus. Enlargement of the nose did not interfere with nasal breathing.

The past and family histories disclosed nothing of significance. There was no history of the ingestion of iodides, bromides, patent medicines,

or excessive amounts of alcohol or tobacco. No symptoms referable to the gastro-intestinal tract had been experienced.

Examination revealed a well-developed and nourished man without abnormal physical findings, except for the condition of the nose

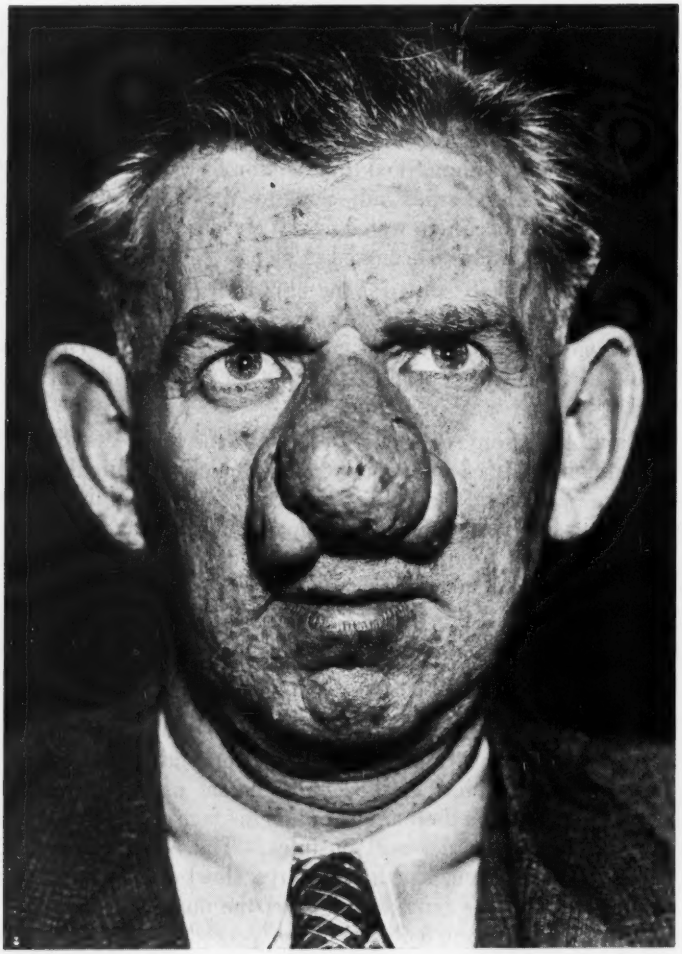

FIGURE 1: Photograph of patient before operation.

(Fig. 1). Many papules, small pustules, and pitted scars were concentrated on the forehead, nose, and adjacent parts of the cheeks and chin. A few comedones were found on the forehead and there were a great many patulous, sebaceous follicles and telangiectases over the entire face.

The beard was involved by a moderate folliculitis. The nose in aggregate was the size of a small lemon and consisted of a large central lobe and a smaller lateral lobe on each side.

Examination of the urine and blood, including complete blood counts and estimation of the level of the blood sugar, and an Ewald test meal

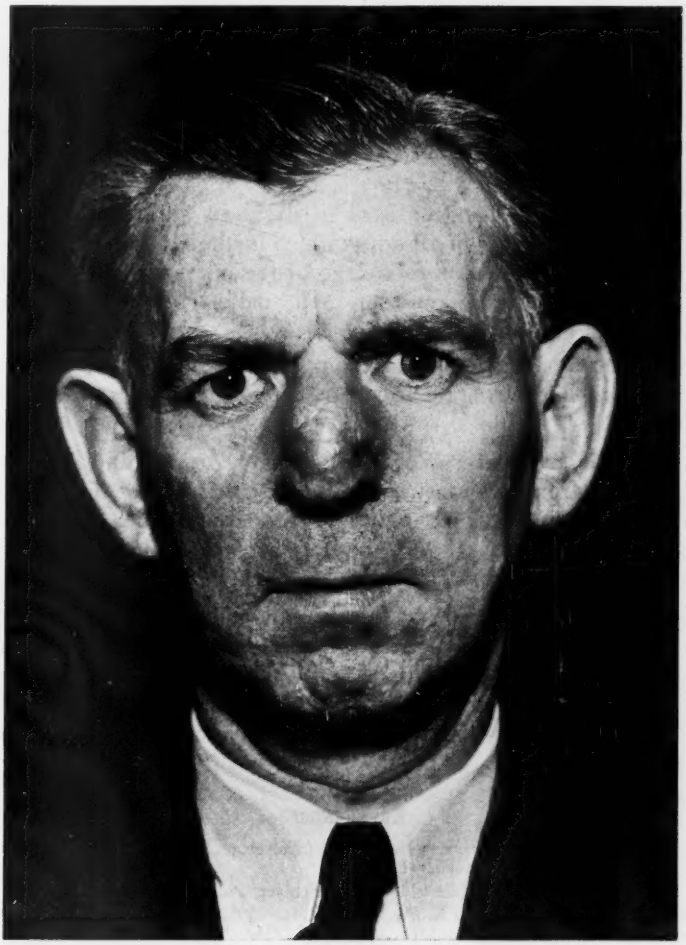

FIGURE 2: Photograph of patient after operation.

gave normal findings. The Wassermann reaction of the blood was negative. Examination of sebum from the enlarged sebaceous glands revealed many Demodex folliculorum.

The patient was admitted to the hospital for surgical removal of the rhinophyma. Local treatments to ameliorate the folliculitis were given before operation.

Because of its unusual size, only the left half of the growth was removed at the first operation. Under avertin and gas-oxygen anesthesia, several straight cutting needles were inserted parallel to the left nostril from the proximal end of the swelling distally to the normal tip of the nose. The needles delineated the outline of a normal nose. The lobule on the left side was excised, leaving the normal ala intact. The left half of the central mass was then excised down to the needles, leaving this half of the nose essentially normal in size and contour. Bleeding was controlled by pressure bandages.

The postoperative care consisted of dry heat administered several times daily and removal of all crusts which hindered smooth epithelialization. Ten days after the first stage of the operation, the right half was removed in a similar manner. The patient made an uneventful recovery from both procedures (Fig. 2).

There are several methods of treating rhinophyma, but the above procedure of simply excising the excess tissue has given a very satisfactory result.

Microscopic sections show numerous deeply penetrating ducts lined by epithelium from which new islands of skin arise. The denuded area is covered with surprising rapidity by epithelium which in color and texture is nearly identical with the normal skin of the nose, a result which is impossible to obtain by the use of skin grafts.

Microscopically, sections of the skin and underlying tissue showed slight thickening and keratosis of the surface epithelium, considerable diffuse edema and chronic inflammation of the underlying stroma, numerous large sebaceous glands extending deeply into the underlying tissues, and several small cysts lined by keratotic squamous epithelium similar to that on the surface.

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MIGRAINE IN A PATIENT WITH ESSENTIAL HYPERTENSION

Report of a Case

C. R. K. JOHNSTON, M. D.

The patient, a married woman 47 years of age, came to the Clinic on October 15, 1937, complaining of right-sided headaches which had been present for eight years and of irregular menses for one year. An interesting observation was that she always had hemicrania on the right side affecting the right temple. These headaches occurred at any time, but usually began when the patient rose in the morning and lasted all day if measures were not taken to obtain relief. No aura preceded the ache, nor was it accompanied by visual disturbance. The headaches were quite severe and had become increasingly more frequent, recurring at intervals of two or three weeks at the time of admission. They were always accompanied by nausea and vomiting. On one occasion the patient had vomited sixteen times in one day and on another occasion ten times. Following the headache, the stools tended to be lighter in color. The patient suspected that several foods such as cheese and beer would provoke a headache.

Other probable manifestations of allergy included a chronic, mucoid postnasal drip and short periods of diarrhea not accompanied by crampy pain. A brother of the patient had migraine and her son had hay fever.

For one year the menses had been irregular and had been characterized by menorrhagia and periods of amenorrhea. She had an occasional "warm feeling" but no other symptom of the menopause. Dyspnea had been noted on exertion, with occasional slight edema of the ankles and mild nocturia.

Physical examination at admission revealed a well-developed and well-nourished individual whose systolic blood pressure was 220 mm. and diastolic pressure 120 mm. of mercury. Three days later a recheck revealed a pressure of 206 mm. systolic and 110 mm. diastolic. Opthalmoscopic examination showed early sclerosis of the retinal arteries but no edema of the discs, exudates or hemorrhages. The lungs were entirely clear, while the heart was slightly enlarged. The rhythm was regular except for a rare premature beat. The mitral first sound was split and the aortic second sound moderately accentuated. The remainder of the physical examination, including the pelvis, was not significant.

Routine urinalysis and blood counts gave normal findings. The level of the blood urea was 45 mg. per 100 cc. and the urea clearance test gave an average of 63 per cent. A roentgenogram of the chest showed

nothing abnormal. The electrocardiogram showed a moderate degree of left axis deviation.

Although the patient had a definite essential hypertension, the character of the headaches strongly suggested that they were due to allergy; therefore complete studies for the determination of allergens were made. These revealed positive skin reactions to a number of foods, notably wheat, milk, eggs, beans, and several other less important foods as well as to several inhalants such as dust, feathers, and orris root.

The patient was instructed regarding a strict regimen for the elimination of inhalants and foods, avoiding all the significant food allergens. Additional calcium and vitamins were prescribed in view of the limited diet. Restricted activity, extra rest, and a mild sedative were advised because of the hypertension.

Seven weeks following the institution of this regimen the patient reported no further headaches. Six months after treatment was begun she returned and reported that she felt much improved. During this interval she had had only four mild headaches, each of which could be traced to a violation of diet, chiefly by the use of milk. There had been no attacks of diarrhea and the postnasal drip had become less troublesome. Although the blood pressure had improved it was still elevated, the systolic pressure varying from 182 to 192 mm. and the diastolic reading from 106 mm. to 112 mm. of mercury. Amenorrhea had been present for more than six months, she was nervous and irritable, and complained of occasional mild hot flashes. The urinary, blood, and electrocardiographic findings showed no significant change.

The final diagnosis was essential hypertension, migraine due to food allergy, and menopause.

Summary

This case is an interesting problem of migraine due to food allergy, occurring in a patient with essential hypertension. Her headaches were well relieved, although there was only a slight decrease in blood pressure and the symptoms of the menopause became worse. Further presumptive evidence of allergy was furnished by the intermittent diarrhea which was relieved following treatment, and the postnasal mucoid drip which improved. A definite familial history of allergy was also present in this case.